THE SYNTHESIS OF PHENAZINES.

A Thesis

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by

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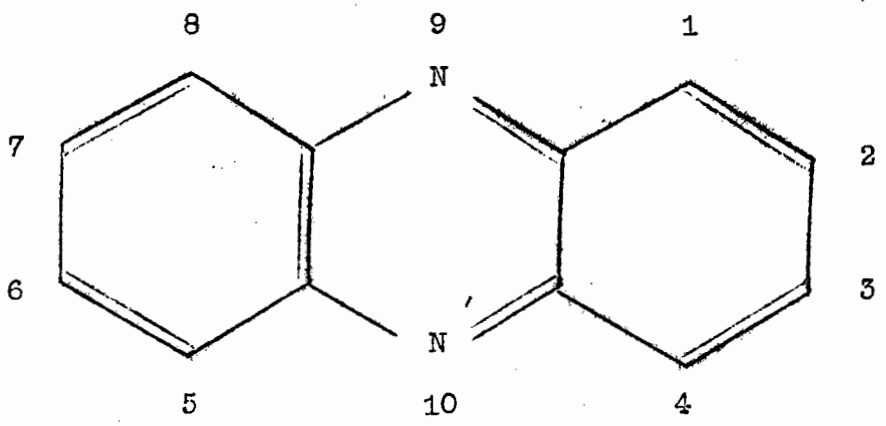
The following system of numbering of the phenazine nucleus was used throughout this thesis.



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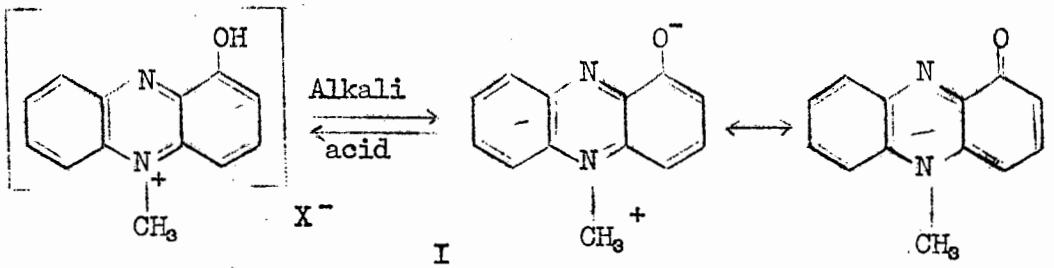
I N T R O D U C T I O N.

During a bacteriological survey of strains of Pseudomonas pyocyanea (Ps. aeruginosa) from cases in Groote Schuur Hospital, Cape Town, it was noticed that a considerable variation in colour production took place on agar slopes. Whereas the normal strains produce green to blue colourations in the agar, due to the production of the phenazine pigment pyocyanin (I), a number of strains produced a red pigment. Red pigment producing strains of



I

Psuedomonas pyocyanea had been noted previously[1] and cursory chemical investigations thereof yielded little information as to the nature of the red pigment, which has been called pyorubin.

Professor F.G. Holliman, in collaboration with various other workers in the Department of Chemistry at the University of Cape Town, is conducting a research programme with the view to the eventual elucidation of its structure. This might prove of interest in relation to that of pyocyanin and to the metabolic activities of the Pseudomonas group of organisms.

Two pigments, called A and B, were isolated from the cultures. Since pyocyanin, the pigment produced by the usual strains of Pseudomonas pyocyanea is a phenazine, it seemed possible that the pigments A and B might also be based on the phenazine nucleus. From studies of the absorption of these pigments in the ultra-violet and visible regions, as compared to that of 1-aminophenazine, it seemed probable, due to the similarity, that the two pigments are

closely related and in all probability identical with regard to the light absorbing systems of their structures, which has either an 1-aminophenazine or closely related system present.

Since these pigments are evidently of the phenazine type, the need for a series of substituted phenazines was felt with a view to (a) studying the effect of substituents upon the ultraviolet and visible absorption spectra and (b) providing a series of reference substances for infra red spectral studies on phenazine compounds. With these results at hand, it was hoped that the prediction of possible structures for these pigments could then be made with more assurance.

The aim of this project was, however, not the elucidation of the structures of these pigments, although this originally provided the incentive for this work.

At the time this programme was started it seemed probable that these pigments contained an amino (or related) group and a hydroxy (or related) group and attention was therefore focussed on phenazines containing these two groups.

Of all the possible amino-hydroxyphenazines, only four were known to have been synthesized up to the end of 1954. These were (i) 2-amino-3-hydroxyphenazine, prepared by Ullmann and Mauthner[2] and also be Kehrmann and Kissine[3]; (ii) 2-amino-7-hydroxyphenazine, prepared by Nietzki and Simon[4], by Ullmann and Gnaedinger[5] and by Kehrmann and Haenny[6]; (iii) 3-amino-7-hydroxyphenazine, prepared by Kehrmann and Haenny[6]; and (iv) 1-amino-2-hydroxyphenazine, prepared by Hegedus[7].

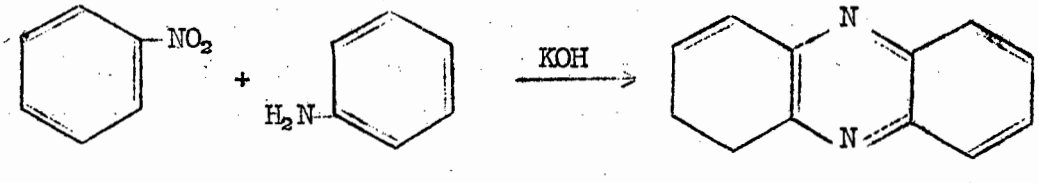
The only amino-methoxyphenazines known to have been synthesized up to the same time were (i) 2-amino-7-methoxyphenazine, prepared by Fischer[8], (ii) 1-amino-3-methoxyphenazine, prepared by

Elderfield et al[9] and (iii) 1-amino-2-methoxyphenazine, prepared by Hegedus[7].

Research in the synthetic phenazine field has largely been dominated by the synthesis of alkoxy- and hydroxyphenazines. A great deal of the interest shown in the hydroxy- and alkoxyphenazines, more especially the disubstituted ones, was due to the discovery of iodinin, the pigment of chromobacterium iodinum by Davies and the work done thereon by Clemo and McIlwain[10]. Iodnin was found to be a dihydroxyphenazine-di-N-oxide, with one of the hydroxy groups in the 1-position. The position of the second hydroxy group was not known, and the search for the position it occupied provided further incentive for research on these phenazines.

Of all the methods by which substituted phenazines may be prepared, as yet, no method is a general one. The method, by which a substituted phenazine is to be prepared, depends not only on the substituent, but also on the position which the substituent must occupy.

Amongst the methods of phenazine synthesis, the method of Wohl and Aue[11], where an aromatic nitro group and an aromatic amine condense ortho to each other, in the presence of a strong base such as potassium hydroxide, to form an azine ring, has been extensively employed. Wohl and Aue[11] obtained phenazine by heating nitrobenzene and aniline together in the presence of dry potassium hydroxide.

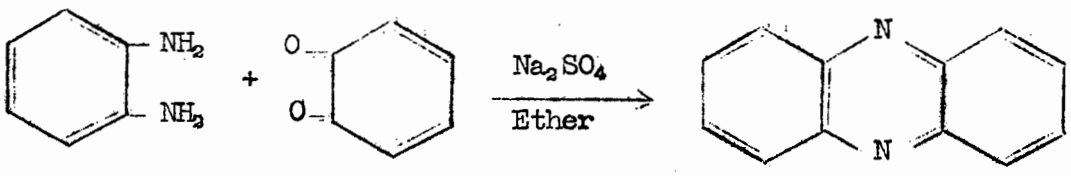


With a substituted aniline or nitrobenzene a substituted phenazine may be obtained. This has been used for the synthesis of alkoxy-

phenazines. Yoshioka[12] isolated 1-methoxyphenazine by heating o-nitroanisole with aniline in the presence of powdered potassium hydroxide. With both substituted aniline and substituted nitrobenzene, the possibility of isomers arises. Both 1,8-diethoxyphenazine and 1,5-diethoxyphenazine were isolated by Serebryanyi and Chernetskii[13] after o-nitrophenetole and o-phenitidine had stood for 3 days with powdered potassium hydroxide. This reaction has been conducted in the cold[13,14], at elevated temperatures[11,15], and at elevated temperatures in an inert solvent[12,16,17]. No aminophenazines have been prepared by this method. In attempting to synthesize an aminophenazine by this method, the introduction of an amino group into either the nitrobenzene, or the aniline, will increase the number of possible isomers and the difficulty of their separation and identification.

The yields obtained in a Wohl-Aue synthesis of a phenazine are usually of the order of about 10%. One of the highest yields obtained by this method was reported by Abramova and Postovskii[18]. They obtained phenazine in a 30% yield by reacting aniline with sodium amide to give N-sodio-aniline (PhNHNa) and then condensed this with nitrobenzene, in xylene at 125°.

Phenazines have been prepared by the condensation of o-diamines with o-quinones according to the method of Hinsberg[19].

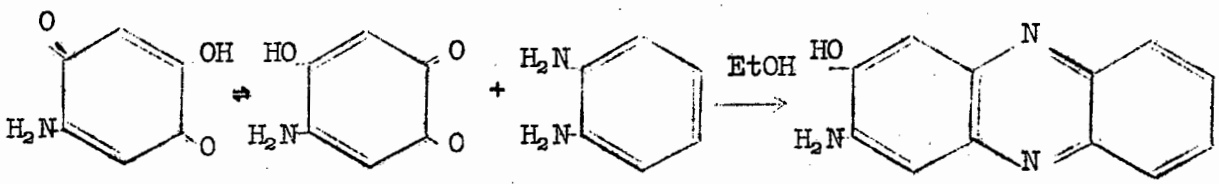


(20)

Thus 1-methoxyphenazine was prepared by the condensation of 3-methoxy-o-quinone with o-phenylenediamine in acetic acid-benzene solution[21], and 2-hydroxyphenazine by the condensation of o-phenylenediamine and 4-hydroxy-o-quinone in acetic acid[22]. Kehrmann and Hoehn[23] prepared

2-acetamidophenazine by the condensation of 4-acetamido-o-quinone and o-phenylenediamine. When both a substituted o-quinone and a substituted o-phenylenediamine are used, the formation of isomers is possible. 1,5-Dimethoxy- and 1,8-dimethoxyphenazine were isolated by Kiprianov et al[24] on condensing 3-methoxy-o-quinone with 3-methoxy-o-phenylenediamine. When 1,2-cyclohexadiones are used in a similar condensation, tetrahydrophenazines are obtained. Dehydrogenation of these phenazines can be achieved by heating with palladium-charcoal[25]. The yield, in a Hinsberg condensation, was found to vary considerably with the substituents. 1,2-Cyclohexadione, in aqueous-alcoholic medium, condensed with 5,6-diamino-guiacol to give a 17% yield of 1-hydroxy-2-methoxy-5,6,7,8-tetrahydrophenazine, and with 3,4-diaminoveratrol to give 1,2-dimethoxy-5,6,7,8-tetrahydrophenazine in 48% yield[25].

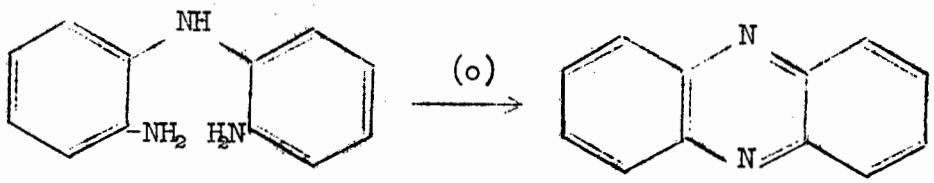
This method has been employed for the synthesis of 2-amino-3-hydroxyphenazine by the condensation of o-phenylenediamine with 2-hydroxy-5-amino-p-benzoquinone in alcohol[3].



Kehrmann and Haenny[6] condensed 4-nitro-o-phenylenediamine with 4-hydroxy-o-quinone in glacial acetic acid medium. Amonst the products obtained, two were 2-nitro-7-hydroxyphenazine and 2-nitro-6-hydroxyphenazine. The 2-nitro-7-hydroxyphenazine was acetylated and this product reduced with zinc in acetic acid to give 2-amino-7-acetoxyphenazine. By hydrolysis of the last product 2-amino-7-hydroxyphenazine was isolated. By a similar series of reactions 2-amino-6-hydroxyphenazine was obtained.

One of the difficulties of this method is the preparation of the o-quinones. Teuber and Staiger[26] have prepared a number of o-quinones from phenols having an alkoxy or an alkyl group in the para position by oxidation with potassium nitrosodisulphonate. From these o-quinones he successfully prepared a number of phenazines by condensation with o-phenylenediamine.

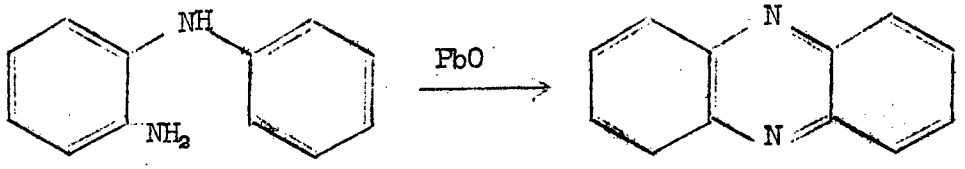
A method which has found considerable application and has the advantage that good yields are normally obtained, is the mild oxidative ring closure of o,o'-diaminodiphenylamines to give a phenazine, by loss of ammonia and oxidation of the intermediate dihydrophenazine. Thus Eckert and Steiner[27] prepared phenazine from o,o'-diaminodiphenylamine by oxidation with either hydrogen peroxide, ferric chloride or potassium permanganate.



Various substituted phenazines have been prepared by this method. Phenazine-2-carboxylic acid was prepared from 2,2'-diaminodiphenylamine-5-carboxylic acid by Kogl et al[28], by oxidation with hydrogen peroxide. Tomlinson[29] prepared some methyl- and methoxyphenazines by oxidizing the corresponding o,o'-diaminodiphenylamines with ferric chloride in hydrochloric acid medium. Hegedus[30] prepared 1-aminophenazine from 2,6,2'-triaminodiphenylamine by this method and Elderfield et al[9], a number of substituted 1-aminophenazines. One of these was 1-amino-3-methoxyphenazine, prepared by the oxidation of 2,6,2'-triamino-4-methoxydiphenylamine with ferric chloride in hydrochloric acid medium.

Ammonia has also been successfully eliminated from two amino groups o,o'- to the amine linkage in diphenylamine to give a phenazine, by heating with acid. By this method Ullmann et al[31] obtained 2-aminophenazine from 2,4,2'-triaminodiphenylamine, and Albert and Duewell[32], 1-aminophenazine from 2,6,2'-triaminodiphenylamine and 1,3-diaminophenazine from 2,4,6,2'-tetraaminodiphenylamine (45% yield). No amino-methoxyphenazines or amino-hydroxyphenazines have been prepared by this method.

A small number of phenazines have been prepared by heating o-aminodiphenylamines with oxidizing agents such as lead oxide, lead dioxide and manganese dioxide. Fischer and Heiler[33] obtained phenazine by heating o-aminodiphenylamine with lead oxide. 2-Aminophenazine was obtained from 2,4'-diaminodiphenylamine by this method[8].

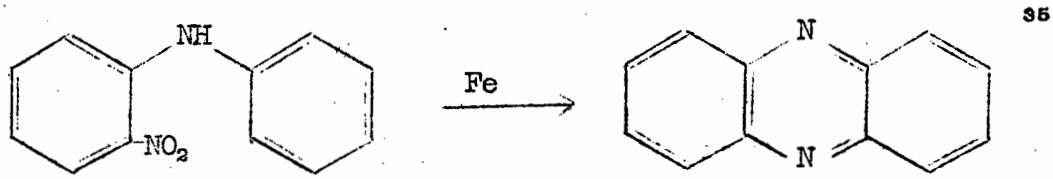


Similarly McCombie et al[34] obtained 2-methoxyphenazine from 2-amino-4-methoxydiphenylamine. 2-Amino-7-methoxyphenazine was obtained from 2,4-diamino-4'-methoxydiphenylamine by this method[8]. Nietzki and Simon[4] prepared 2-amino-7-hydroxyphenazine by heating an ammonia solution of 2,4-diamino-4'-hydroxydiphenylamine with manganese dioxide. Phenazine and not 1-methoxyphenazine was obtained on heating 2-amino-2'-methoxydiphenylamine with lead dioxide[34]. The methoxy group is eliminated in preference to a hydrogen atom and the ring closed in that position. Yields of phenazine obtained by this method were usually poor[34,35].

Waterman and Vivian[35], on consideration of this method of synthesis, were led to the idea that "the whole procedure of reduction of the 2-nitrodiphenylamine to the amino compound followed by oxidation of

this to phenazine might be replaced by a new reaction: a reduction of the nitrocompound which gave no opportunity for amine formation, but which would take place under conditions favourable to direct ring closure".

The method, patented by Waterman and Vivian[36] of heating o-nitrodiphenylamines with an "oxygen acceptor" such as carbon, ferrous oxalate or one of various metals has now found considerable application in the synthesis of phenazines with a variety of substituents, but mostly for alkoxy- and halo-phenazines.



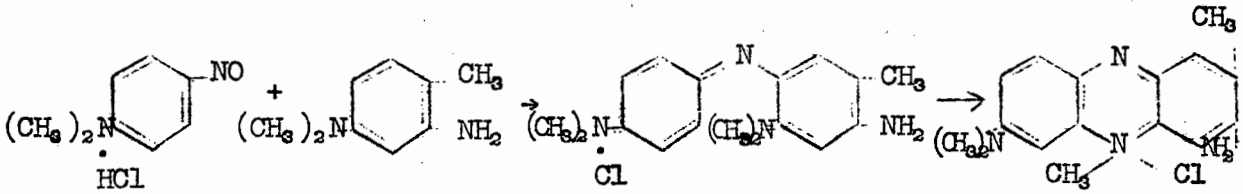
[35]

Slack and Slack[37] stated that when ring closure can occur alternatively at positions occupied by an alkoxy group or a H atom, the alkoxy group is preferentially eliminated and the ring closed in that position. A similar preferential elimination of a nitro group to a hydrogen atom was noted by Waterman and Vivian[35]. Phenazine was obtained on heating both 2-nitro-2'-methoxydiphenylamine and 2,2'-dinitrodiphenylamine with iron[35]. This method being so closely related to that of Fischer it is not surprising to find similar eliminations taking place during ring closure. In order to prevent the elimination of an alkoxy group, in the synthesis of alkoxyphenazines by this method, such a group must not be in the o'-position in the o-nitrodiphenylamine.

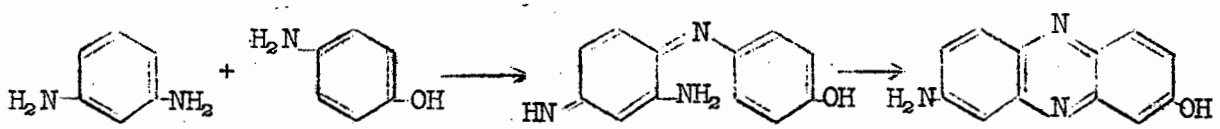
Slack and Slack[37] obtained 1-methoxyphenazine from 2,3-dimethoxy-2'-nitrodiphenylamine. Vivian[38] found that in the reductive ring closure of o-nitrodiphenylamines in the preparation of substituted phenazines, isomers may be formed where the possibility exists, e.g. both 2-chloro-6-ethoxyphenazine and 2-chloro-7-ethoxyphenazine were

obtained on heating 4-chloro-3'-ethoxy-2-nitrodiphenylamine with granulated lead and ferrous oxalate. No nitromethoxy- or amino-methoxy or the corresponding hydroxyphenazines have been prepared by this method. Vivian[39] has prepared 1-aminophenazine from 2-nitro-6-aminodiphenylamine. Yields of up to 95%[38] have been obtained by this method.

A method which has not often found direct application to the synthesis of phenazines, but may in fact form an intermediate step in the synthesis of phenazine by methods such as the oxidation of o-aminodiphenylamines, is the preparation of phenazines from indamines or anil type of compounds. Cohen and Crabtree[40] prepared more complex phenazines by this method, in some cases isolating the indamine before effecting the ring closure. Thus they prepared 2-methyl-3-amino-7-dimethylaminophenazinium methochloride from 2-aminodimethyl-p-toluidine and p-nitrosodimethylaniline hydrochloride in 50% acetic acid solution, ring closing the intermediate indamine by heating. The following series of reactions were involved.



2-Amino-7-hydroxyphenazine[5] was obtained in a 70% yield by bubbling air through an ammonia solution of the anil obtained from m-phenylenediamine and p-aminophenol.



Other aminohydroxyphenazines which have been isolated are 2-amino -3-hydroxyphenazine which was obtained with a little 2,3-diamino-phenazine on treating o-phenylenediamine with ferric chloride in hydrochloric acid medium[2] and previously mentioned 2-amino-7-hydroxy-phenazine, obtained by the desulphonation of 2-amino-7-hydroxy -phenazino-6-sulphonic acid[41].

Indirect routes have been employed in other syntheses of simple amino- and hydroxyphenazines. The attaining of these compounds has been preceded by the preparation of a substituted phenazine and then followed by conversion of the substituent to the hydroxy or amino group.

Hydroxyphenazines have been prepared predominantly by the dealkylation of alkoxyphenazines. Dealkylation being effected either by heating with hydrobromic acid[21,42,43], hydrobromic acid in acetic acid[12,15,26], sulphuric acid[43] or with aluminium chloride in benzene[44].

The conversion of an 1-amino to a 1-hydroxyphenazine has not been readily accomplished via diazotisation[7,45]. Amino groups in a 2-position have been successfully diazotised. Albert and Duewell[32], by this method, removed the 3-amino group from 1,3-diaminophenazine and Kehrmann and y'Punti[46] the 2-amino group from 2-amino-6-acetamido-phenazinium phenyl chloride. The acid hydrolysis of amino to hydroxy groups has found considerable application in this field. This conversion has been effected by heating with phosphoric acid[30], sulphuric acid[7,47] and hydrochloric acid[48].

The importance of this conversion lies in the fact that the orientation of an unknown amino-, diamino- or amino-hydroxyphenazine may be determined by its conversion to one of the well known dihydroxyphenazines.

Aminophenazines have been obtained by replacement reactions. Albert[32] obtained 1-aminophenazine from 1-hydroxyphenazine, by heating with ammonia in phenol with cupric acetate as catalyst. The chloro

groups in chloro substituted phenazines have also been successfully replaced by hydroxy groups[49] and by alkoxy groups[50]. Successful replacements of halogen by amino groups have been accomplished; by Pachter and Kloetzel[50], who obtained a small yield of 2-aminophenazine from 2-chlorophenazine by heating with ammonia and by Vivian[39] who accomplished replacement in good yield by heating with ammonia, using cuprous chloride as catalyst.

With the object of preparing an aminophenazine, nitro groups may be introduced on to the phenazine nucleus. Up to the end of 1954 only five papers had appeared (A.C.A.) on the nitration of phenazines. Claus[51] reported obtaining a nitrophenazine, probably 2-nitrophenazine by boiling phenazine with fuming nitric and sulphuric acids. Kehrmann and Havas[52] obtained 1,3-dinitrophenazine on nitration of phenazine with concentrated nitric and sulphuric acid. By nitration of 5,10-diacetyl-5,10-dihydrophenazine they obtained 2-nitrophenazine and 2-nitro-5,10-dihydro-5,10-diacetylphenazine, affecting the nitration in acetic acid. Albert and Ducwell[32] repeated the nitration of phenazine and obtained a mixture of 1-nitrophenazine and a dinitrophenazine, which they suggested was probably 1,8-dinitrophenazine. By hydrogenation these nitrophenazines were converted to the corresponding aminophenazines.

Hegedus[7], by nitration of 2-methoxy- and 2-hydroxyphenazine with potassium nitrate in concentrated sulphuric acid at 0°, obtained 1-nitro-2-methoxy- and 1-nitro-2-hydroxyphenazine respectively. From these two products a series of phenazines were obtained, which included the 1-amino-2-methoxy- and the 1-amino-2-hydroxy derivatives, prepared by hydrogenation of the corresponding nitro compounds.

The aim of this research programme was to prepare, by various methods, some new amino-hydroxy-, amino-methoxy- and related phenazines and to determine the effect of substituents on the ultra-violet and visible absorption spectra.

DISCUSSION.

SECTION IA.

For the purpose of preparing 1-methoxyphenazine, pyrogallol 1-monomethyl ether and o-phenylenediamine were required as starting materials. Pyrogallol 1-monomethyl ether could be prepared from pyrogallol, by the method of Hillemann[53], or from o-vanillin, by the method of Surrey[54]. The method of Surrey is the better of the two, but, as no o-vanillin was available and could not be successfully prepared from guiacol by the Reimer-Tiemann method or by the method of Duff[55], Hillemann's method was attempted. However, this method was not successful as on adding calcium chloride to the solution of pyrogallol 1-monomethyl ether, after hydrolysis of the pyrogallol 1-monomethyl ether carbonate, the product decomposed, due to the presence of alkali in the clacium chloride.

o-Vanillin was obtained and by a Dakin type of reaction converted to pyrogallol 1-monomethyl ether[54].

1-Methoxyphenazine was prepared by the method of Surrey[21] and the product isolated found to be pure enought to use for further work without recrystallisation.

At the time of starting this problem the only phenazines which were known to have been nitrated were, phenazine itself, 9,10-diacetyl -9,10-dihydrophenazine, 2-hydroxyphenazine and 2-methoxyphenazine. The first two at elevated temperatures with nitric and sulphuric acid[51,52,32], and the last two at 0° with potassium nitrate in sulphuric acid[7].

This last method was used for the nitration of 1-methoxyphenazine. An excess of potassium nitrate above that required for mono-nitration was left to stand with a solution of 1-methoxyphenazine in sulphuric

acid at 0°. A mononitro-1-methoxyphenazine was obtained in theoretical yield. Originally it was not known into which position the nitro group had entered the phenazine nucleus, but from the following argument the 4-position seemed the most probable.

From the results of Albert and Duewell[82] who on nitration of phenazine with concentrated nitric and sulphuric acids found the nitro group to enter in the 1-positions only, this was later supported by Maffei and Aymon[56], either the 4-, 5- or 8-position seemed the probable position into which the nitro group had entered. Due to the positive mesomeric effect of the methoxy group, the ring to which it is attached will be more susceptable to electrophilic attack by the nitronium ion than the unsubstituted ring and the 4-position therefore seemed the likely position into which the nitro group had entered. However, the 5-, 8- and also the 2-positions could not be completely ruled out.

It was proved later that the nitro group had entered into the 4-position, thus giving 1-methoxy-4-nitrophenazine.

1-Methoxyphenazine was also nitrated by nitric acid in acetic anhydride. A 25% yield of 1-methoxy-4-nitrophenazine was obtained by this method, during a 5 hour reaction period, as compared to an almost quantative yield by nitration with potassium nitrate in sulphuric acid during a 14 hour reaction period.

It was not until this problem was well under way that the existence of a paper by Otomasu[57], describing the nitration of 1-methoxyphenazine became known. The methods used by Otomasu were similar to those developed independently in this laboratory. Where identical compounds to his were isolated, it will be indicated in the discussion. The melting point of his 1-methoxy-4-nitrophenazine was 224°; the product isolated here had a melting point of 225° - 6°.

For the proof of the orientation of the methoxy-nitrophenazine

and hence of all the phenazines obtained therefrom, it was necessary to obtain from this product a dihydroxyphenazine, the orientation of which could be proved by comparison with other well known 1-substituted dihydroxyphenazines.

By catalytic hydrogenation of 1-methoxy-4-nitrophenazine in glacial acetic acid using Adam's catalyst, an almost colourless solution of 9,10-dihydro-1-methoxy-4-aminophenazine was obtained. By shaking this solution vigorously in the air, oxidation of this product to 1-methoxy-4-aminophenazine took place, the solution turning dark red. (In all the hydrogenations of phenazines conducted, unless specifically stated otherwise, this same procedure, of shaking in the air to oxidise the 9,10-dihydro compound, was followed). By the addition of alkali the solution was neutralised and the precipitated 1-methoxy-4-amino-phenazine isolated. The isolated product after recrystallisation from petroleum either had a melting point of 211° - 3°. Otomasu conducted this hydrogenation in methanol with palladium oxide as catalyst and obtained a product of melting point 214°, after recrystallisation from benzene.

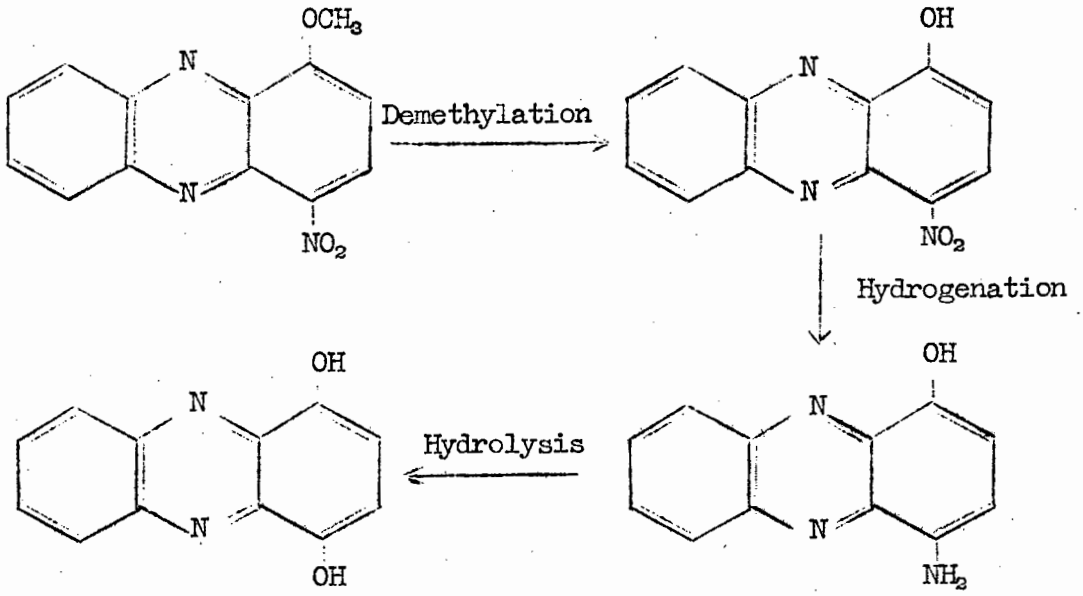
1-Methoxy-4-acetamidophenazine (m. pt. 232° - 3°; Otomasu m. pt. 231°) was obtained on acetylation of 1-methoxy-4-aminophenazine with acetic anhydride at room temperature.

By heating 1-methoxy-4-aminophenazine with acid under fairly mild conditions it was hoped to achieve both demethylation of the methoxy group and hydrolysis of the amino group, to give a dihydroxyphenazine, without too much decomposition. This could not be accomplished by refluxing with 3 N sulphuric acid. On refluxing for 4 hours unchanged 1-methoxy-4-aminophenazine was obtained and on refluxing for 14 hours, no product could be isolated.

Otomasu was found to have achieved the conversion of 1-methoxy-4-aminophenazine to 1,4-dihydroxyphenazine by heating with 25%

hydrochloric acid at 180° for 8 hours. On attempting to repeat this conversion a product of melting point 167° - 180° was isolated. This melting point did not agree with that of any of the 1-substituted dihydroxyphenazines. As this was evidently not a pure compound it was hoped that by acetylation of this product, followed by recrystallisation some separation of the products would be achieved. However, after recrystallisation of the acetylated product it had a melting point of 179° - 195° as compared to 193.5° - 4°, the melting point given[44] for 1,4-diacetoxyphenazine. Other than saying there might have been some 1,4-diacetoxyphenazine present, no conclusion could be arrived at.

Another method of preparation of a dihydroxyphenazine therefore had to be attempted. The method which presented itself is indicated in the following scheme.



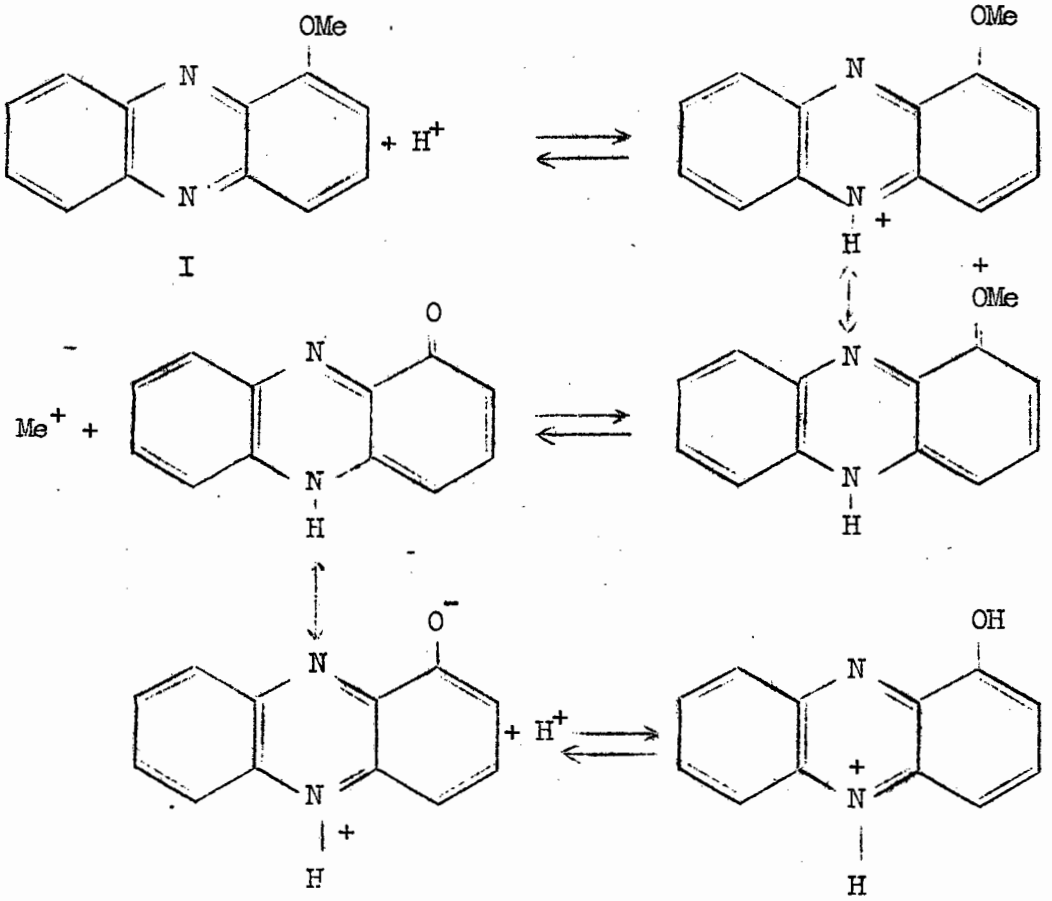
1-Alkoxyphenazines have been dealkylated without apparent difficulty by heating with 48% hydrobromic acid[21], hydrobromic acid in acetic acid[12] or with anhydrous aluminium chloride[44] in benzene. 1-Methoxyphenazine could be demethylated without difficulty by heating with

48% hydrobromic acid[21]. Otomasu[57] converted 1-nitro-2-methoxyphenazine to 1-nitro-2-hydroxyphenazine by heating with hydrobromic acid in acetic acid. Various other alkoxyphenazines have been successfully dealkylated by acidic reagents.

The acid cleavage reactions of ethers are assumed to proceed through oxonium salts, of a structure such as R_2OH^+, by the following scheme.

$$R_2O + H^+ \rightarrow R_2OH^+ \rightarrow ROH + R^+$$

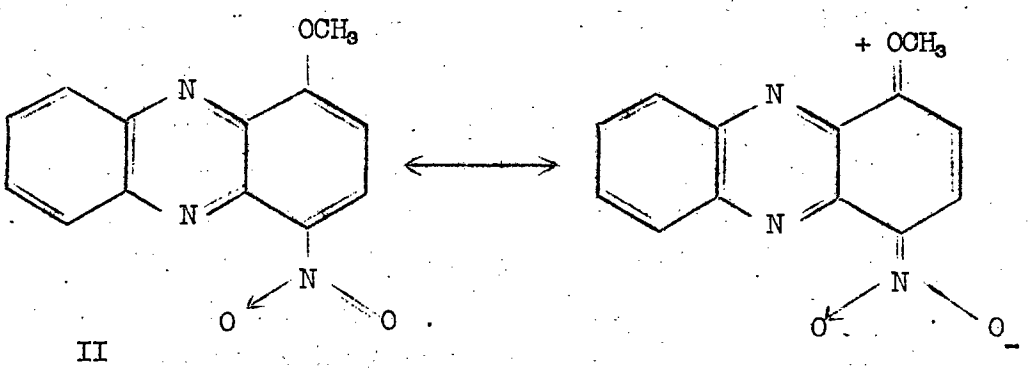
It is possible that an alternative, though similar mechanism, may operate in the cleavage of an alkoxyphenazine. Under acid conditions the ring nitrogen atom will pick up a proton, before the ethereal oxygen, to give normal salt formation. In the case of 1-methoxyphenazine (I) the following mechanism may operate:



On heating 1-methoxy-4-nitrophenazine with 48% hydrobromic acid for periods varying from ½ hour to 4 hours, the product precipitated from the solution on neutralisation, could not be purified by recrystallisation or vacuum sublimation and was found to be alkali insoluble. This product gave a positive Lassaigne test for halogen. Demethylation was not achieved by hydrobromic acid in acetic acid or by aluminium chloride in benzene either. The failure to cleave the ether linkage of 1-methoxy-4-nitrophenazine (II) by acidic reagents must be due to the presence of the nitro group in the 4-position.

The presence of the nitro group will decrease the basicity of the nitrogen atom and thus inhibit a mechanism of the type described above.

Further, when such a group as the nitro is para to a methoxy group in an aryl nucleus, the lone pair of electrons on the oxygen atom is partially donated to the aromatic nucleus by contributions of structures such as III.



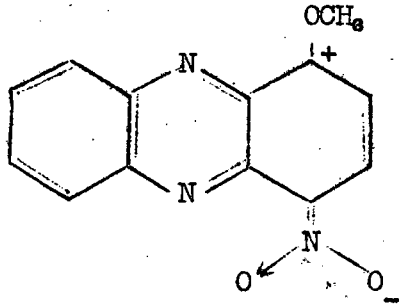
II III

The decreased electron density on the ethereal oxygen atom would decrease the ease of attack by electrophilic, acidic reagents at that centre.

Due to the decreased basicity of the molecule as a whole by the introduction of the nitro group, it now offers no position for ready electrophilic attack. The inhibiting effect of the nitro group on cleavage of the ether linkage by acidic reagents may be illustrated by the results of Gulyayeva and Nikiforova[58]. They found that o-nitro-

anisole was cleaved at only one thirteenth the rate that anisole was cleaved by hydrobromic acid.

On the other hand, the presence of the nitro group will decrease the electron density at the ring carbon to which the methoxy group is attached, by contribution of a structure such as indicated by IV, and enhance the attack by a nucleophilic group on that carbon atom.

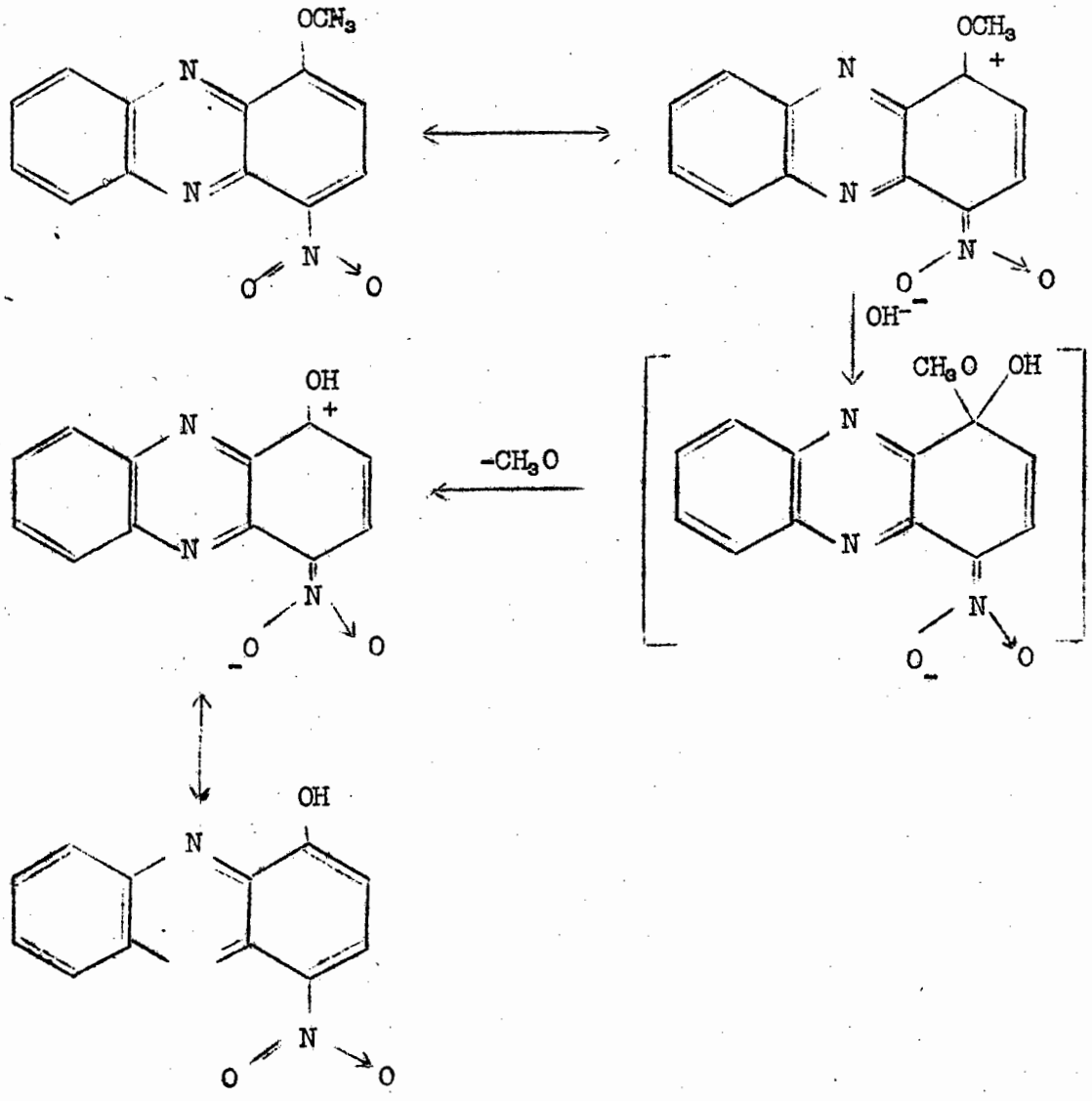


IV

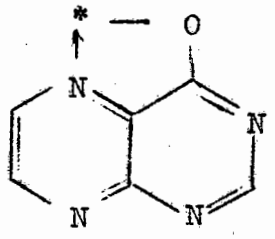
Demethylation, more correctly, demethoxylation of compounds of a similar nature, by nucleophilic attack, has been accomplished. Diphenyl ether due to its weakly basic nature was not cleaved by strong acids[59], but reacted slowly with aqueous sodium hydroxide at 300°[60]. Kauffmann and Fritz[61] obtained 2-nitro-4-methoxyphenol from 2-nitro-4-methoxyanisole on heating with aqueous-alcoholic potassium hydroxide. A similar observation was made by Oliverio[62]. This effect of nitro groups was also observed by Salkowski[63] who obtained picramide by warming methyl and ethyl picryl ethers with ammonia.

An almost quantitative yield of 1-hydroxy-4-nitrophenazine was obtained by effecting the demethylation of 1-methoxy-4-nitrophenazine by refluxing with an aqueous-alcoholic potassium hydroxide solution.

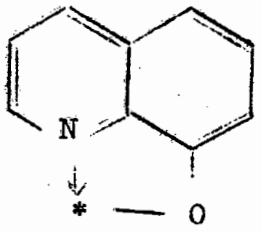
The following possible mechanism for the demethylation of 1-methoxy-4-nitrophenazine by the nucleophilic attack of the hydroxyl ion is advanced.



It was found that on adding a solution of the potassium salt of 1-hydroxy-4-nitrophenazine to solutions of a number of cations, coloured precipitates were obtained. 4-Hydroxypteridine and 8-hydroxyquinoline, with a similar relation of the hydroxy group to the nitrogen atom, also give complexes with certain cations. These complexes are of the nature indicated by V and VI respectively. The cations are indicated by * in the illustrations V and VI.

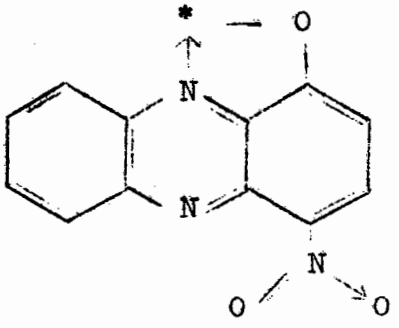


V

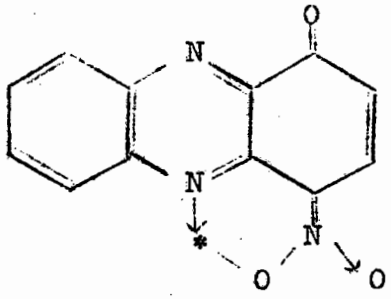


VI

In the case of 1-hydroxy-4-nitrophenazine the cation may have a similar position, as indicated by VII, but there is also the possibility that the cation may be situated as in VIII.

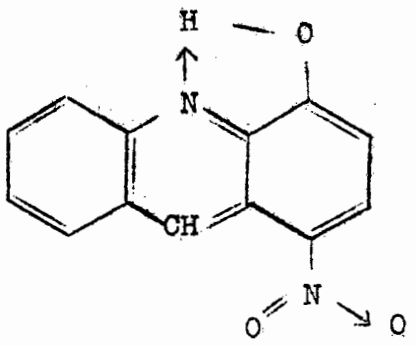


VII

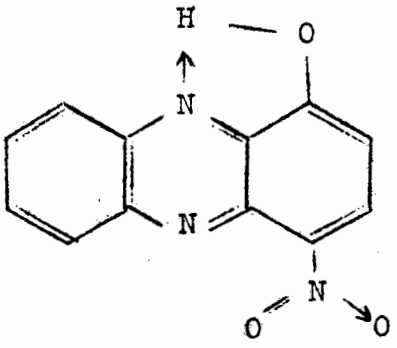


VIII

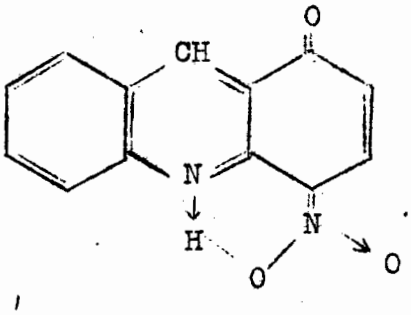
It is hoped to investigate these two possibilities in the future by X-ray analysis of the potassium salt of 1-hydroxy-4-nitrophenazine. By preparing 1-hydroxy-4-nitro- and 1-nitro-4-hydroxyacridine and investigation of their abilities to give precipitates with cations, and by comparing their absorption spectra with that of 1-hydroxy-4-nitrophenazine, it is hoped further information in this respect will be obtained. If the absorption spectra of 1-hydroxy-4-nitroacridine (IX) and 1-hydroxy-4-nitrophenazine are similar, then probably 1-hydroxy-4-nitrophenazinehas a structure such as (X), due to possible similar hydrogen bonding.



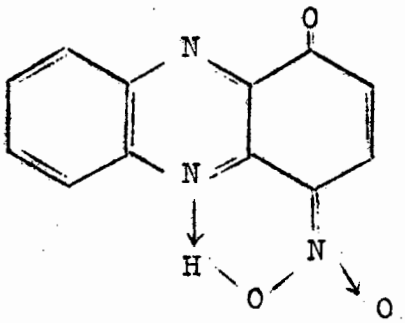
IX



X



XII



XIII

If on the other hand 1-nitro-4-hydroxyacridine (XII) has a similar absorption spectra, then a structure such as XIII seems likely, due to the similarity in probable hydrogen bonding.

Other phenazines have been reported to react with cations. 2,3-Diaminophenazine[64] gave coloured precipitates, although of a different type to that of 1-hydroxy-4-nitrophenazine, with a number of cations. 1-Hydroxyphenazine polymerised[65] with copper to form characteristic fibres.

The yellow crystals of 1-hydroxy-4-nitrophenazine dissolved in benzene and cyclohexane to give yellow solutions, but in hydroxylic solvents such as methanol and ethanol, reddish solutions were obtained. Dissolved in acetone a yellow solution is obtained turning reddish on dilution with water. Tautomerism, hydrogen bonding and

perhaps ionisation could account for this. An alcoholic solution of 1-hydroxy-4-nitrophenazine was found not to obey the Beer-Lambert law.

Crystals of 1-hydroxy-4-nitrophenazine on exposure to the atmosphere change from yellow to reddish.

1-Acetoxy-4-nitrophenazine was readily obtained from 1-hydroxy -4-nitrophenazine by heating with acetic anhydride and sodium acetate.

Hydrogenation of 1-hydroxy-4-nitrophenazine gave 9,10-dihydro -1-hydroxy-4-aminophenazine which was readily oxidised to 1-hydroxy -4-aminophenazine. Under otherwise identical conditions, the hydrogenation was found to proceed approximately twice as rapidly in dilute alkaline solution as in glacial acetic acid solution. 1-Hydroxy-4-aminophenazine could not be isolated by ether extraction, after it had been precipitated from the acetic acid solution by adding alkali, due to decomposition during the extraction and evaporation of the ether. The product obtained by this method was alkali insoluble. On attempting to recrystallise this product from ethyl acetate, the material separating on cooling the hot solution, would not redissolve on heating. The mother liquors on standing lost their colour and deposited an amorphous sediment which could not be redissolved.

Crude 1-hydroxy-4-aminophenazine was isolated by hydrogenating 1-hydroxy-4-nitrophenazine in dilute alkaline solution, oxidising the 9,10-dihydro compound by shaking in air, neutralising the solution with acetic acid and filtering off the precipitated 1-hydroxy-4-amino-phenazine. This product could not be successfully recrystallised from any of the solvents tried. Recrystallisation could be effected from water, but the recovery was poor and the product not stable for any length of time. 1-Hydroxy-4-aminophenazine was found to be especially unstable in alkaline solution, probably due to its possible quinonoid structure making it susceptable to oxidation.

The best method of isolating 1-hydroxy-4-aminophenazine was the following: Immediately the hydrogenation was ceased, acetic acid was added to the alkaline solution and the precipitated 9,10-dihydro -1-hydroxy-4-aminophenazine filtered off and dried in vacuo. By this method decomp osition of the product was minimised and good yields obtained. Complete oxidation of the 9,10-dihydro compound was effected, before derivatives of 1-hydroxy-4-aminophenazine were prepared, by shaking up in the solvent to be used.

By this procedure a good yield of 1-acetoxy-4-acetamidophenazine was obtained. Dry 9,10-dihydro-1-hydroxy-4-aminophenazine was shaken up in glacial acetic acid to effect the oxidation, acetic anhydride and sodium acetate added and the mixture then refluxed. Heating with acetic anhydride only, also gave 1-acetoxy-4-acetamidophenazine.

This product was also prepared, in almost quantative yield by a Chattaway type of acetylation of 9,10-dihydro-1-hydroxy-4-amino-phenazine. Acetic anhydride was added to a cold alkaline solution of 9,10-dihydro-1-hydroxy-4-aminophenazine in a nitrogen atmosphere. 9,10-Dihydro-1-acetoxy-4-acetamidophenazine separated almost instantaneously and during removal by filtration and subsequent recrystallisation was oxidised to 1-acetoxy-4-acetamidophenazine. This product is readily hydrolysed by both dilute acid and alkali.

When crude 1-hydroxy-4-aminophenazine was acetylated in acetic anhydride at room temperature only 1-hydroxy-4-acetamidophenazine was obtained.

1-Acetoxy-4-aminophenazine was prepared by the hydrogenation of 1-acetoxy-4-nitrophenazine. This hydrogenation was conducted in glacial acetic acid. After oxidation of the 9,10-dihydro compound, the 1-acetoxy-4-aminophenazine was precipitated by the gradual neutralisation of the solution with sodium hydroxide. Many attempts were made to repeat this preparation, only one proved successful.

In most cases the product eventually precipitated had an amorphous appearance and an indefinite melting point. A possible explanation could be that during the neutralisation of the acetic acid solution local heating and local high alkali concentration hydrolysed the acetoxy group, giving the unstable 1-hydroxy-4-aminophenazine. On neutralisation of the acetic acid solution with concentrated ammonia solution, in an attempt to keep the final volume small, local heating could be observed and although the temperature of the mixture as a whole never exceeded 25°, no product could be isolated.

A similar observation was made by Kehrmann and Haenny[6] on preparing 2-amino-7-acetoxyphenazine by the reduction of 2-nitro-7-acetoxyphenazine with zinc dust and glacial acetic acid. On neutralisation of their acetic acid solution with ammonia solution, 2-amino-7-hydroxyphenazine was isolated, but on neutralisation with sodium bicarbonate, no hydrolysis took place and 2-amino-7-acetoxyphenazine was isolated. The product precipitated on neutralisation of the acetic acid solution with sodium bicarbonate, after hydrogenation of the 1-acetoxy-4-nitrophenazine, had to be vacuum sublimed before it could be successfully recrystallised.

1-Acetoxy-4-nitrophenazine was not successfully reduced with zinc dust and acetic acid in the cold or at elevated temperatures. On first adding the zinc dust to the acetic acid solution a purple colour developed but disappeared after a while. The excess zinc dust and sludge were filtered off, but on neutralisation of the filtrate no definite product was obtained.

Hegedus[7] converted 1-amino-2-hydroxyphenazine to 1,2-dihydroxyphenazine by refluxing with 3 N sulphuric acid for 16 hours. It was hoped similar conditions would convert 1-hydroxy-4-aminophenazine to 1,4-dihydroxyphenazine and the orientation of the series thus be proved.

The product precipitated, by neutralisation of the sulphuric acid

solution, after refluxing 1-hydroxy-4-aminophenazine with the sulphuric acid for 16 hours was purified by vacuum sublimation. The sublimate was found to melt at 181° - 3° with subsequent resolidification and finally melt at 231° - 3° with decomposition. By a comparison of these melting points with those of the 1-substituted dihydroxyphenazines, it was found that only 1,4-dihydroxyphenazine (m. pt. 230°) had a melting point in this vicinity. The final high melting point was taken as an indication that 1,4-dihydroxyphenazine had probably been formed.

It was hoped, by acetylation and subsequent recrystallisation, to separate the products of the reaction and obtain 1,4-diacetoxyphenazine, identify it, and thus determine the orientation.

The sublimate was acetylated by (i) refluxing with acetic anhydride and sodium acetate and also by (ii) acetic anhydride in pyridine. In neither case could a pure compound be isolated by recrystallisation alone. The melting point of the acetylated product obtained by the first method, after recrystallisation, was 168° - 193° and that obtained by the second method 172° - 180°.

On gradual growing of the crystals, on recrystallisation of the product of (ii), two distinct types of crystals were observed. Crystals answering to the description of 1,4-diacetoxyphenazine (tarnished golden needles) by King et al[44] were handpicked from the mixture. The melting point of these crystals was found to agree with that of 1,4-diacetoxyphenazine and on admixture with 1,4-diacetoxyphenazine, prepared later, no depression of the melting point was observed.

The crystals remaining after removal of the greater part of the 1,4-diacetoxyphenazine still had to be identified. After recrystallisation, these crystals had a melting point of 173° - 203°, melting rapidly at 198° - 203°.

Although the product isolated after the acid treatment of the hydroxy-aminophenazine did not have a melting point near that of 1,2-dihydroxyphenazine [m. pt. 270° - 5° [7]], the material obtained on acetylation thereof started melting in the vicinity of the melting point of 1,2-diacetoxyphenazine (m. pt. 168° [7]). As the 2-position was also a possible position into which the nitro-group might have intered on nitration of 1-methoxyphenazine, the fear arose that perhaps a mixture of the 1,4- and the 1,2-isomers had been formed on nitration of the 1-methoxyphenazine and that recrystallisation had failed to separate them in subsequent steps. To investigate this possibility a polarographic reduction of 1-methoxy-4-nitrophenazine was done, a potentiometric titration of 1-hydroxy-4-nitrophenazine and paper chromatograms of all the compounds prepared. In all these investigations the presence of only one compound was indicated.

Those crystals remaining after removal of the 1,4-diacetoxy-phenazine were eventually predicted to be impure 1-acetoxy-4-acetamido-phenazine. They were found to melt most rapidly at 198° - 203°, i.e. quite near the melting point of 1-acetoxy-4-acetamidophenazine [m. pt. (190°) 205° - 210°]. The colour changes observed on heating these crystals with dilute acid and alkali were found to be similar to those of 1-acetoxy-4-acetamidophenazine but different from those of 1,4-di-acetoxyphenazine.

If this prediction was correct, then there should have been unchanged 1-hydroxy-4-aminophenazine present in the sublimate obtained, after the acid treatment of the 1-hydroxy-4-aminophenazine. 1-Hydroxy-4-aminophenazine had a melting point of 190° - 4°, followed by resolidification. The sublimate had a similar temporary melting point at 181° - 3°. Assuming this melting point to be depressed, due to the presence of the other product, it appears that 1-hydroxy-4-aminophenazine might have been present in the sublimate.

More vigorous conditions than those employed here were deemed

necessary to achieve the desired conversion.

The conversion of 1-hydroxy-4-aminophenazine to 1,4-dihydroxyphenazine was achieved by heating with 3 N sulphuric acid at 148° for 17 hours. The 1,4-dihydroxyphenazine could be purified by sublimation alone. Acetylation of 1,4-dihydroxyphenazine with acetic anhydride and pyridine gave 1,4-diacetoxyphenazine.

The melting points of both these products agreed with that quoted in the literature for 1,4-dihydroxy- and 1,4-diacetoxyphenazine.

	Found	Given
1,4-Dihydroxyphenazine m. pt.	234° - 6°	230°[57]
1,4-Diacetoxyphenazine m. pt.	193° - 6°	193.5° - 4°[44]

Due to the agreement of these melting points the orientation of these compounds was accepted as 1,4.

Hegedus[7], on nitration of 2-hydroxyphenazine, under conditions similar to those employed in the successful nitration of 2-methoxyphenazine, obtained 1-nitro-2-hydroxyphenazine. Under similar conditions to those used for the nitration of 1-methoxyphenazine, 1-hydroxyphenazine gave no definite product. The presence of 1-hydroxy-4-nitrophenazine and unchanged 1-hydroxyphenazine in the product was detected by paper chromatograms, but could not be isolated.

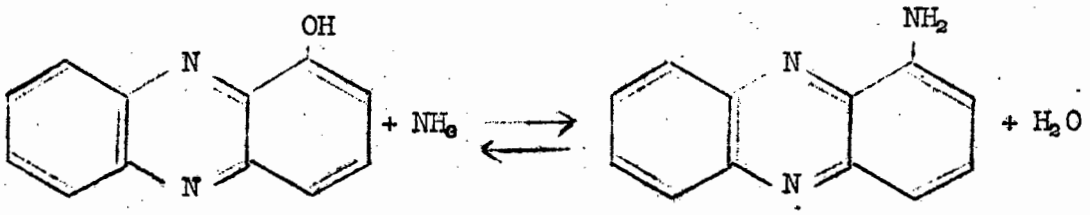
1-Acetoxyphenazine could not be nitrated by fuming nitric acid in acetic anhydride; at 0° unchanged 1-acetoxyphenazine was recovered and at room temperature the 1-acetoxyphenazine was decomposed.

1-Acetamidophenazine was prepared by the method of Cookson[66]. Bishydroxyiminocyclohexanone and o-phenylenediamine were boiled together in water and the resultant 1,2,3,4-tetrahydro-1-hydroxyimirophenazine both dehydrogenated and acetylated, to give 1-acetamido-

phenazine, by refluxing with acetic anhydride. The bishydroxyimino-cyclohexanone required in this preparation was prepared by the method of Borsche[67]. Borsche did not describe the synthesis in detail and as it was found that this preparation had to be conducted with great care to be successful, the preparation is described in some detail in the experimental section. Unless the acetyl chloride and isoamyl-nitrite were added extremely slowly to the cyclohexanone, the temperature of the reaction mixture, which should be maintained below 0°, rose rapidly and the product decomposed. An attempt to prepare bishydroxyiminocyclohexanone from cyclohexanone, sodium nitrite and hydrochloric acid was not successful.

1-Acetamidophenazine was readily hydrolysed to 1-aminophenazine by dilute hydrochloric acid.

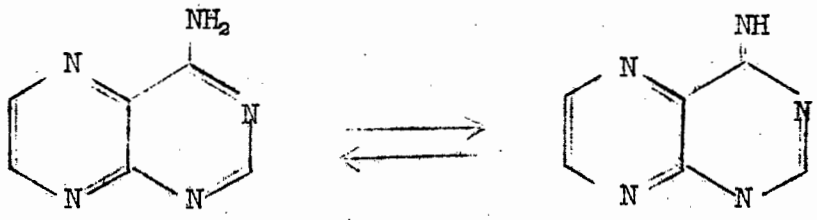
Albert and Duewell[82] had found that 1-hydroxyphenazine could be converted to 1-aminophenazine by heating with ammonia in phenol with cupric acetate as catalyst. If this reaction involves an equilibrium,



it was argued, that by heating 1-aminophenazine with water in excess the equilibrium might be displaced in the reverse direction. No 1-hydroxy-phenazine, however was isolated by this method.

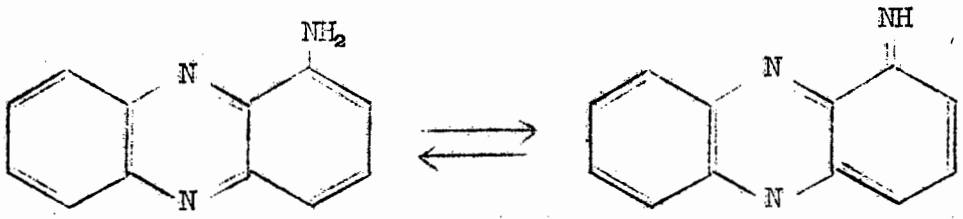
1-Aminophenazine could not be converted to 1-hydroxyphenazine via diazotisation in the usual manner or via diazotisation in glacial acetic acid using nitrosyl sulphuric acid. The product obtained by

the last method was recrystallised just as 1-hydroxyphenazine. The melting point of this product was 155° - 161° as compared to 152° - 4° for 1-hydroxyphenazine. On admixture of the two, however, the melting point was depressed to 123° - 126°. The failure to diazotise the 1-amino group may perhaps be explained partly in a manner similar to that used for explaining the failure to diazotise 4-aminopteridine (XIV), i.e. the amino group forms part of an amidine system (XV).



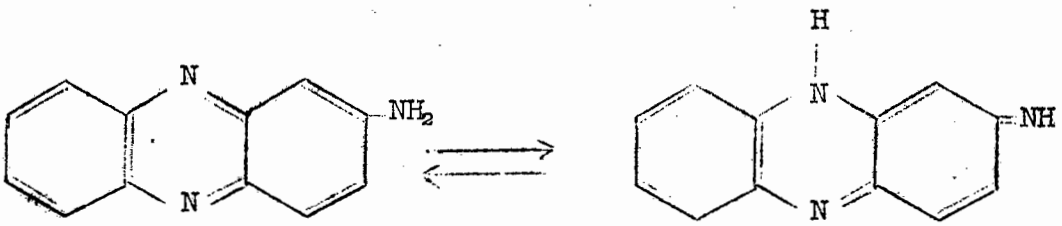
XIV XV

Thus for 1-aminophenazine (XVI) the structure (XVII) may be written



XVI XVII

2-Aminophenazine (XVIII) for which a similar structure may be written (XIX) has, however, been successfully diazotised [32,68,69].



XVIII XIX

A possible factor may be that the amino group in the 1-position takes part in hydrogen bonding with the 9-nitrogen atom of the azine ring. The 2-amino group is not capable of such hydrogen bonding.

1-Aminophenazine was not susceptable to alkaline hydrolysis but by acid hydrolysis, the successful conversion of 1-aminophenazine to 1-hydroxyphenazine, as conducted by Hegedus[30], was successfully duplicated.

A conversion of 1-aminophenazine to 1-hydroxyphenazine was achieved by the Bucherer reaction. 1-Aminophenazine was heated with a sodium bisulphite solution under pressure at 148° for 8 hours and the addition product decomposed by boiling in alkali. A large amount of unchanged 1-aminophenazine was accompanied by a small amount of 1-hydroxyphenazine. The smell of ammonia on decomposing the addition product and the colour reactions in alkali supported the evidence of paper chromatograms that 1-hydroxyphenazine had been formed. More vigorous conditions could possibly increase the yield.

1-Acetamidophenazine was nitrated at 0° with fuming nitric acid in acetic anhydride. The product isolated was found to be a mono-nitro derivative of 1-acetamidophenazine, but originally, the position into which the nitro group had entered was not known. A similar argument to that used in the case of 1-methoxyphenazine may be used here for suggesting the probable position into which the nitro group had entered. As with 1-methoxyphenazine the 4-, 5- and 8- were the most probable positions into which the nitro group had entered. Due to the electromeric effect of the acetamido group, the 2- position could not be excluded, but the 4-position appeared the most favoured for attack by the nitronium ion and the product was assumed to be 1-acetamido-4-nitrophenazine. This was in fact proved to be the orientation later.

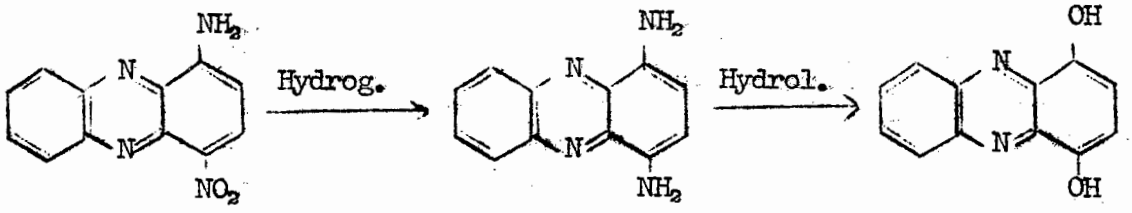
On recrystallisation of the crude nitrated product from alcohol, the yield dropped from the theoretical to 25% after three

recrystallisations. The melting point rose from 230° - 6° to 272° - 4°. Acetone raised the melting point even more rapidly and correspondingly the recovery was even poorer. No definite product could be isolated from the mother liquors on evaporation. Recrystallisation from toluene failed to raise the melting point higher than 244° - 6°.

Under apparently identical conditions to those employed for several successful nitrations of 1-acetamidophenazine, on one occasion no 1-acetamido-4-nitrophenazine could be isolated.

By acid hydrolysis of 1-acetamido-4-nitrophenazine, 1-amino-4-nitrophenazine was prepared. This could be reconverted to 1-acetamido-4-nitrophenazine by refluxing with acetic anhydride and glacial acetic acid.

It was hoped to orientate this product by the conversion to a known dihydroxyphenazine. The method by which it was hoped to achieve this was: Hydrogenation of the 1-amino-4-nitrophenazine (XX) would give 1,4-diaminophenazine (XXI) and this by acid hydrolysis would be converted to 1,4-dihydroxyphenazine (XXII) and the orientation thus determined.



XX XXI XXII

On hydrogenation of 1-amino-4-nitrophenazine in glacial acetic acid an almost colourless solution of 9,10-dihydro-1,4-diaminophenazine was obtained. On oxidation a dark solution was obtained. This was neutralised by the careful addition of alkali and extracted with ether. On evaporation of the ether only an amorphous decomposed product was obtained.

Crude 1,4-diaminophenazine was isolated by filtration after neutralisation of the acetic acid solution. On attempted recrystallisations the product decomposed and could therefore not be isolated in a pure state. That it had been prepared was proved by the acetylation of the crude 1,4-diaminophenazine by acetic anhydride at room temperature when 1,4-diacetamidophenazine was isolated.

1,4-Diaminophenazine could not be converted to 1,4-dihydroxyphenazine by heating with 3 N sulphuric acid for 17 hours.

As the orientation of this compound could not be proved by conversion to the dihydroxyphenazine, another method was attempted. It was argued that the diaminophenazine was either the 1,4- or, perhaps, the 1,2-diaminophenazine, and that if it was the 1,2-diamino compound it should give the Hinsberg condensation with o-quinone or 1,2-diketo compounds. This crude diaminophenazine did not condense with o-quinone, diacetyl or benzil and the 1,2-orientation was therefore considered unlikely.

As the orientation of those phenazines originating from the mononitro compound obtained on nitration of 1-acetamidophenazine could not be determined by the methods tried, some other method had to be adopted. As those phenazines originating from the nitrated 1-methoxyphenazine were all known to have a 1,4-orientation, the conversion of any of these to any of the phenazines originating from the nitro-acetamidophenazine or vice versa, would prove that the nitro-acetamidophenazine also had a 1,4-orientation.

An attempt to hydrolyse the amino group of 1-amino-4-nitrophenazine to a hydroxy group, by heating with acid, thereby giving 1-hydroxy-4-nitrophenazine, was not successful.

Semiganowski[70] found that amino groups ortho and para to a nitro group could be determined by heating such a compound with 25% sodium hydroxide; ammonia was liberated and the amino group converted to a

hydroxy group.

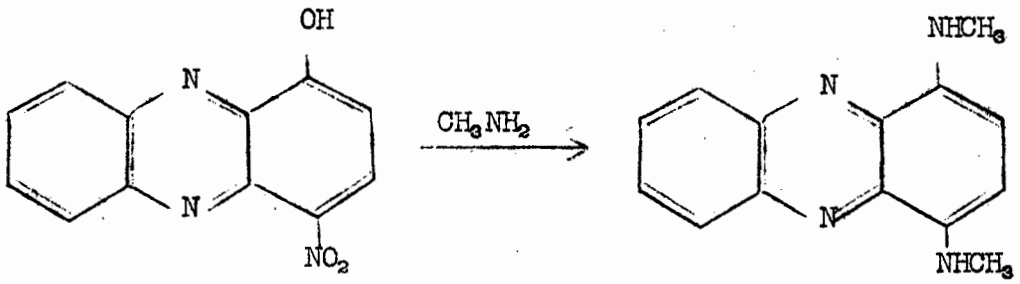
1-Amino-4-nitrophenazine, obtained by the hydrolysis of 1-acetamido-4-nitrophenazine, was refluxed for 45 minutes with 6 N sodium hydroxide. The smell of ammonia was noticed and 1-hydroxy-4-nitrophenazine isolated. This product gave no depression of the melting point on admixture with a sample of 1-hydroxy-4-nitro phenazine prepared from 1-methoxy-4-nitrophenazine (known orientation). The behaviour of these two compounds was identical on paper chromatography.

A tie up between these two series was also effected by the conversion of 1-hydroxy-4-nitrophenazine to 1-amino-4-nitrophenazine. 1-Hydroxy-4-nitrophenazine was converted to 1-amino-4-nitrophenazine by heating with an aqueous-alcoholic solution of ammonia. The product isolated here gave no depression of the melting point on admixture with a sample of 1-amino-4-nitrophenazine obtained by the hydrolysis of 1-acetamido-4-nitrophenazine. By the above reversible conversions of 1-amino-4-nitrophenazine to 1-hydroxy-4-nitrophenazine the orientation of the nitro-acetamidophenazine was found to be 1,4. A further argument supporting this will be advanced in the discussion of the absorption spectra of these series of phenazines.

On heating 1-methoxy-4-nitrophenazine with an aqueous-alcoholic solution of ammonia at 110° - 130° hydrolysis of the methoxy group and conversion of the resultant 1-hydroxy-4-nitrophenazine to 1-amino-4-nitrophenazine took place. At 200° no product could be isolated.

It was hoped that on heating 1-hydroxy-4-nitrophenazine with an aqueous-alcoholic solution of methylamine, under similar conditions to those just described, 1-methylamino-4-nitrophenazine would be obtained. The product isolated after this treatment, on analysis, did not satisfy the values required. No oxygen was found to be present. This analysis was found to agree with that required for 1,4-dimethylaminophenazine. On acetylation of this product with acetic anhydride and pyridine, at room temperature, the acetylated material

satisfied the analysis required by 1,4-di-methylacetamidophenazine. From these results it appears that, on heating 1-hydroxy-4-nitrophenazine with an aqueous-alcoholic solution of methylamine, not only is the hydroxy group, but also the nitro group, replaced by a methylamino group.



1,4-Dimethylaminophenazine was found to decompose on exposure to the atmosphere. It could be recrystallised from petroleum ether but in all other solvents tried it decomposed. 1,4-Di-methylaminophenazine was also obtained by heating 1-methoxy-4-nitrophenazine with an aqueous-alcoholic solution of methylamine.

No product was isolated on heating 1-hydroxy-4-nitrophenazine with an aqueous-alcoholic dimethylamine solution.

1-Hydroxyphenazine, where there is no activating nitro group, could not be converted to 1-aminophenazine by heating with an aqueous-alcoholic solution of ammonia and neither 1-hydroxy- nor 1-methoxyphenazine could be converted to 1-methylaminophenazine by heating with an aqueous-alcoholic solution of methylamine.

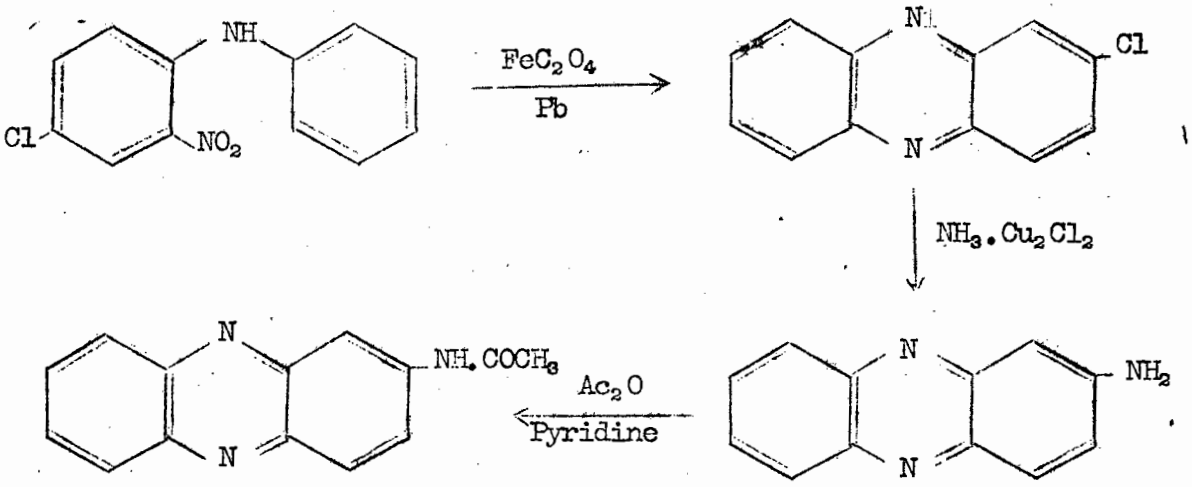
Albert and Duewell[32] found that 1-hydroxyphenazine could be converted to 1-aminophenazine by heating in phenol with ammonia and cupric acetate. This method was adapted for the preparation of 1-methylaminophenazine. Instead of passing ammonia gas through, the 1-hydroxyphenazine was heated in a sealed tube with methylamine, phenol and cupric acetate. The hydroxy group in 1-hydroxy-4-nitro-

phenazine could not be replaced by the methylamino group on similar treatment. Heating 1-hydroxyphenazine with dimethylamine under these conditions did not give 1-dimethylaminophenazine.

SECTION IB.

As both 1-methoxyphenazine and 1-acetamidophenazine were successfully nitrated, and as Hegedus[7] found the nitration of 2-methoxyphenazine to proceed readily, an attempt was made at the nitration of 2-acetamidophenazine.

The following scheme was the method followed for the preparation of 2-acetamidophenazine.



2-Chlorophenazine was prepared from 2-nitro-4-chlorodiphenylamine by heating with granulated lead and ferrous oxalate[71].

2-Aminophenazine was not obtained on passing ammonia through a hot mixture of 2-chlorophenazine and phenol in the presence of cupric

acetate. Pachter and Kloetzel[50] prepared 2-aminophenazine from 2-chlorophenazine in 13% yield by heating in an ammonia solution at 200°. Vivian[39] replaced halogen atoms in the 2-position of the phenazine nucleus in a number of compounds, in good yield, by heating with ammonia solution, under pressure, in the presence of cuprous chloride catalyst. On heating 2-chlorophenazine with concentrated ammonia solution at 200°, for 24 hours, in the presence of a little cuprous chloride, the theoretical yield of crude 2-aminophenazine was obtained. After 4 hours appreciable conversion had already taken place. In a shaking vessel complete conversion was achieved in 12 hours time under these conditions.

After recrystallisation of the 2-aminophenazine, a melting point of 277° - 80° was recorded. Pachter and Kloetzel[50] quote a melting point of 265° - 7°, Ullman et al[31] a melting point of 290° - 1° and Fischer[8] a melting point of 274°.

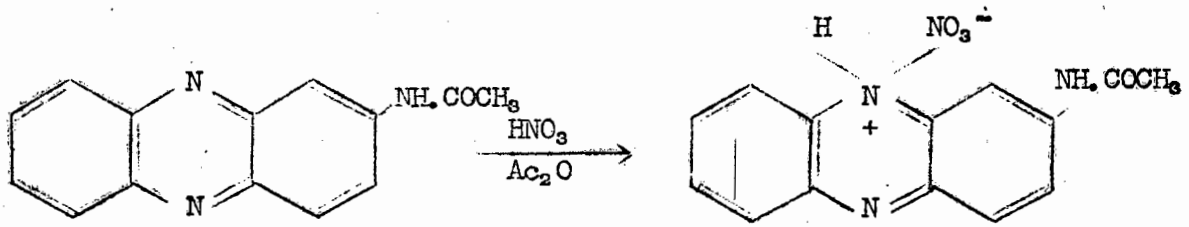
Cohen and Crabtree[40] claimed to have prepared 2-acetamidophenazine by heating 2-aminophenazine with acetic anhydride and sodium acetate but did not quote a melting point. Kehrmann and Hoehn[23] could not repeat this preparation, but claimed to have prepared 2-acetamidophenazine by acetylation of 2-aminophenazine with acetic anhydride and zinc chloride. Their product was found to decompose without melting at 280°.

A product of melting point 195° - 220°, was obtained on acetylating 2-aminophenazine by the method of Cohen and Crabtree[40]. Although apparently not a pure compound, an analysis was done. The results did not agree with those required by 2-acetamidophenazine. An attempt to prepare 2-acetamidophenazine by the method of Kehrmann and Hoehn[23] was also unsuccessful. Neither refluxing 2-aminophenazine with acetic anhydride and pyridine, nor treatment with acetyl chloride and pyridine gave the desired product.

2-Acetamidophenazine was prepared by heating 2-aminophenazine with acetic anhydride and pyridine on a water-bath for 45 minutes. This product was recrystallised from methanol and a melting point of 231° - 4° recorded. On analysis, the results agreed with those required by 2-acetamidophenazine with one molecule of water attached. On heating this product at 100° in vacuo the loss in weight was found to correspond to a loss of one molecule of water per molecule of $C_{14}H_{11}N_3O.H_2O$.

Successful acetylations were also achieved by the above reagents, at room temperature over a long period, and also by refluxing 2-aminophenazine with acetic acid and acetic anhydride.

On attempting to nitrate 2-acetamidophenazine with fuming nitric acid at room temperature or below, in either acetic acid or acetic anhydride, or in acetic acid solution in the presence of sulphuric acid, 2-acetamidophenazinium nitrate was obtained.



Proof that it was 2-acetamidophenazinium nitrate was, its ready solubility in water, that by the addition of alkali to the aqueous solution 2-acetamidophenazine was precipitated and that on hydrolysis of the compound, either by dilute acid or alkali, 2-aminophenazine was obtained.

Attempted nitrations at elevated temperatures resulted in decomposition of the 2-acetamidophenazine.

One of the possible reasons for the failure to nitrate 2-acetamido-

phenazine could be the following: On adding nitric acid to the acetic acid or acetic anhydride solution of 2-acetamidophenazine, 2-acetamidophenazinium nitrate precipitates, due to its insolubility under these conditions. In this state nitration will not be able to proceed so readily. In contrast to this, 1-acetamidophenazine, under similar conditions, gave no precipitate and was successfully nitrated.

2-Methylaminophenazine was prepared by a method similar to that used in the preparation of 2-aminophenazine. 2-Chlorophenazine was heated at 160° - 170° with a 40% aqueous solution of methylamine in the presence of cuprous chloride. At 200°, no product could be isolated. The results of analysis of 2-methylaminophenazine were found to vary remarkably. Due to the similarity in the colour reactions of this product with that of 2-aminophenazine, in acid solution and due to the similarity of their absorption curves, there was no doubt that this was 2-methylaminophenazine, but its purity was open to speculation.

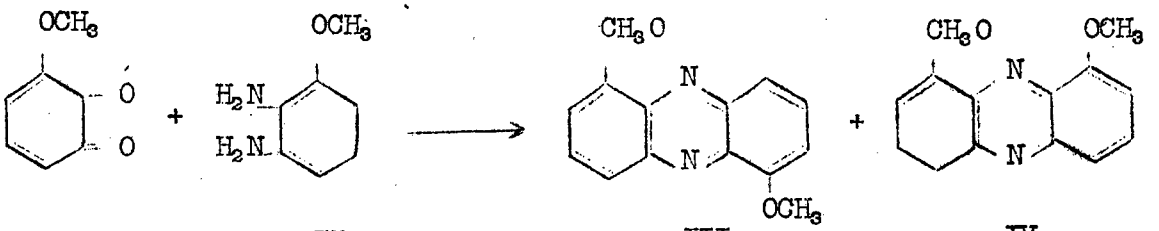
An attempt was made to prepare a phenazine containing both an amino group and a carboxyl group, for comparison with the pigments. No product was isolated on attempting a condensation of 2-chlorophenazine with glycine.

SECTION II.

As the methoxy group activates the ring to which it is attached so that on the nitration of 1-methoxyphenazine, 1-methoxy-4-nitrophenazine is obtained and on the nitration of 2-methoxyphenazine, 1-nitro-2-methoxyphenazine is obtained, methods other than nitration of a methoxyphenazine had to be employed for the preparation of nitromethoxyphenazines with the two groups attached to different rings. Thus for the preparation of a methoxyaminophenazine with the methoxy and the amino groups attached to different rings, via the corresponding nitromethoxyphenazine, the most suitable method appeared to be the

Hinsberg condensation of a methoxy substituted o-quinone and a nitro -o-phenylenediamine.

Theoretically two isomers are possible in a condensation of this nature. Thus Clemo and Daglish[25], on condensation of 3-methoxy-o-quinone (I) with 3-methoxy-o-phenylenediamine (II) in a benzene solution, in the presence of a little glacial acetic acid, obtained both 1,5- (III) and 1,8-dimethoxyphenazine (IV).

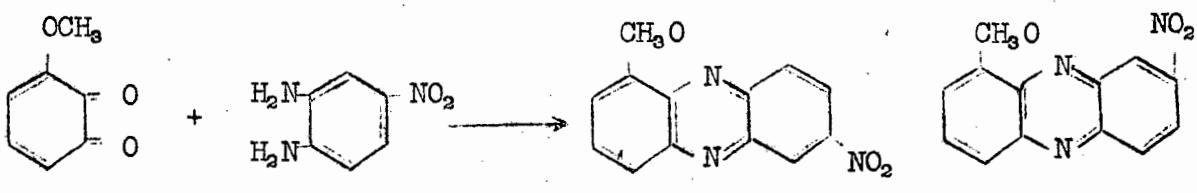


I II III IV

They separated the isomers by chromatography on alumina with benzene as eluting solvent. Separation of the above two isomers has also been achieved by formation of their picrates[24]. The 1,8-isomer forms a picrate poorly soluble in alcohol. This condensation can be compared with the Isay reaction for the preparation of pteridines by condensing a 4,5-diaminopyrimidine with a 1,2-dicarbonyl compound. Two isomers can also arise in Isay's reaction when the dicarbonyl compound is not symmetrical. The proportion of the isomers is influenced by the pH. The orientation depends on electronic influences exerted by both the pyrimidines and the dicarbonyl compounds and the reason for the orientating effect of acidity in these condensations has been attributed to the known higher basic strength of a 4- compared with a 5-aminopyrimidine[72].

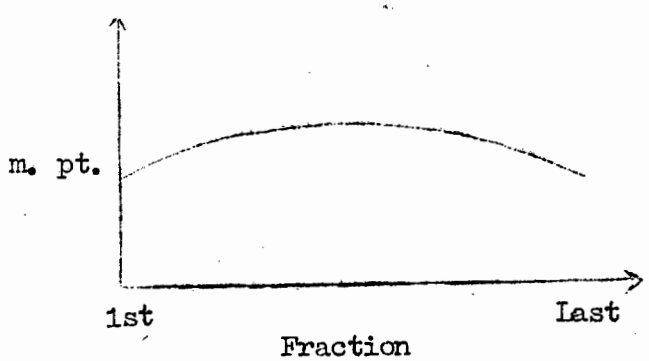
The condensation of 3-methoxy-o-quinone (prepared by the method of Surrey[21]) with 4-nitro-o-phenylenediamine was effected by adding the 4-nitro-o-phenylenediamine (V) dissolved in a large volume of acetic

acid, to the benzene solution of 3-methoxy-o-quinone (I). By this condensation the formation of 1-methoxy-6-nitro- (VI) and 1-methoxy -7-nitrophenazine (VII) was possible.



I V VI VII

For the separation of these possible isomers, the benzene solution, after washing out the acetic acid and drying, was passed through an alumina column and the adsorbate eluted with dry benzene. The eluate was collected in fractions, the benzene evaporated and the melting points of the residues determined. The melting points of the first and last fractions were found to be lower than those of the middle fractions. The following figure illustrates this:

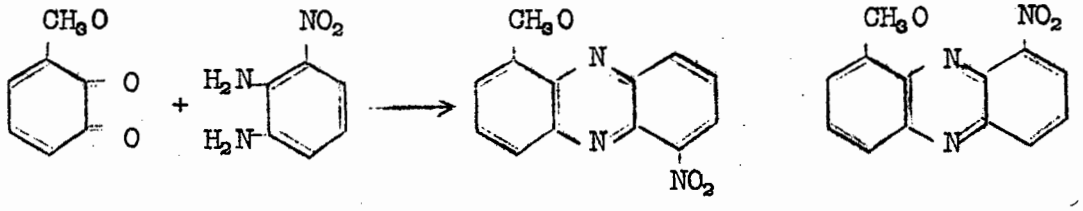


From this figure it seemed probable that only one of the isomers had been formed. The middle fraction, being best separated from impurities has the highest melting point. If isomers were present it would have been expected that the middle fractions would have the lowest melting points and the first and the last fractions, where separation of the isomers had been effected, to have higher melting points.

Further evidence that only one of the isomers had been formed was sought by paper chromatography. With all the solvents tried, however, no definite conclusion could be arrived at, as the spot moved close to the solvent front. As this compound did not give a picrate, no separation along those lines could be attempted.

Attempts to hydrogenate this 1-methoxy-6(or 7)-nitrophenazine with palladium-charcoal catalyst in either absolute alcohol or glacial acetic acid failed. Due to the failure to obtain the corresponding amino-methoxyphenazine by hydrogenation, this condensate could not be orientated by comparison with 1-methoxy-6-aminophenazine, prepared by an unambiguous route. This failure to hydrogenate the compound was later found to be due to poisoning of the hydrogenator.

3-Methoxy-o-quinone (I) and 3-nitro-o-phenylenediamine (VIII) (prepared from 2,6-dinitroaniline[73] by reduction with sodium polysulphide) were condensed under similar conditions to the above condensation. Both 1-methoxy-5-nitro- (IX) and 1-methoxy-8-nitrophenazine (X) were possible products of this condensation.



I VIII IX X

The washed and dried benzene solution of the condensate was chromatographed through alumina, using benzene as eluting solvent and the eluate collected in fractions. On evaporation of the benzene from the various fractions, the residues were all found to have approximately the same melting point and on individual recrystallisation of each of these fractions they attained the same melting point. Apparently only one of the possible isomers was formed under the conditions employed in this condensation.

In both the above condensations it was noticed that, when during the chromatographic purification, the yellow zone, which was the nitro-methoxyphenazine, was stopped moving for any length of time, a dark zone developed on the alumina where the yellow band had been stationary. On elution of this dark band with water, a precipitate was obtained on adding acid to the aqueous eluate; this precipitate was soluble in alkali. Possibly demethylation may take place on the alumina to give a hydroxynitrophenazine. This product would be soluble in alkali but too weakly basic to be dissolved in the acid concentration which could be attained by adding concentrated hydrochloric acid, in a practical volume, to the dilute aqueous eluate obtained.

Hydrogenation of the nitro-methoxyphenazine in glacial acetic acid in the presence of Adam's catalyst gave 9,10-dihydro-1-methoxy-5(or 8)-aminophenazine which was readily oxidised to 1-methoxy-5(or 8)-amino-phenazine.

When an attempt was made to determine whether isomers were present or not, by paper chromatography of both the methoxy-nitrophenazine and the methoxy-aminophenazine, the spots moved close to the solvent front with all the solvents employed and no conclusive indication as to the presence or absence of isomers was obtained.

Due to the failure of all the methods of attempting to prepare 1-methoxy-8-aminophenazine by an unambiguous route, as described later in this thesis, the product of hydrogenation could not be compared with a compound of known orientation.

An attempt was next made to condense 4-methoxy-o-quinone with, first 3-nitro-o-phenylenediamine and then with 4-nitro-o-phenylene-diamine. 4-Methoxy-o-quinone was prepared by the method of Teuber and Staiger[26] by the oxidation of quinol monomethyl ether[74] by potassium nitrosodisulphonate[75].

4-Methoxy-o-quinone and 3-nitro-o-phenylenediamine could not be successfully condensed in a benzene-acetic acid solution. A condensation was first attempted in relatively concentrated solution without success. As it had been noted[30] that the quinones have an oxidising action on the diamines and is more pronounced the higher the concentration, this condensation was repeated in more dilute conditions.

After removal of the acetic acid from the solutions, the benzene solution was passed through an alumina column and eluted with benzene. Here again the yellow band of adsorbed material was found to react on the alumina, leaving a dark band. Only a very small amount of material of indefinite melting point was obtained from the eluate on evaporation of the benzene.

Kehrmann and Haenny[6] successfully condensed 4-hydroxy-o-quinone with 4-nitro-o-phenylenediamine in glacial acetic acid to obtain 2-nitro -7-hydroxy- and 2-nitro-6-hydroxyphenazine and separated these products and the byproducts in the condensation by the difference in their basicities. Condensation of 4-methoxy-o-quinone and 4-nitro-o-phenylenediamine was attempted under their conditions. No pure product was isolated by filtration of the acetic acid solution or by precipitation from the acetic acid by dilution.

The failure to achieve condensations of 4-methoxy-o-quinone with either 3-nitro-o-phenylenediamine or 4-nitro-o-phenylenediamine is rather inexplicable. Teuber and Staiger[26] condensed 4-methoxy-o -quinone with o-phenylenediamine in chloroform solution to give 2-methoxyphenazine.

Unless the 4-methoxy-o-quinone is not stable under the conditions used in these attempted condensations, or decomposed during preliminary operations, no reason for this failure can be advanced. It may be added, that due to the large amount of black sludge separating at the interface of the water and benzene layers, when washing the solutions, it does appear that decomposition takes place.

SECTION IIIA.

This section was embarked on soon after the work on Section II had been started. The products obtained by the Hinsberg condensations could, in each of the four cases in Section II, be one of two possible isomers, in fact it had been expected that both isomers would be formed. A method for the orientation of these products therefore had to be devised.

These products could have been orientated by their conversion to dihydroxyphenazines and comparing their melting points with those of the well known dihydroxyphenazines.

Originally it had been intended to use the nitro-methoxyphenazines obtained by the condensations in Section II to develope into series of phenazines, as had been done in Section I from 1-methoxy-4-nitro-phenazine. Due to the low yields obtained in the case of the condensations involving 3-methoxy-o-quinone another method was proposed.

An alternative method of orientating these compounds was the preparation of one of the possible isomers, or a derivative thereof, by an unambiguous method. By comparison of this product with the condensate, either by their similarity or dissimilarity, the orientation of the condensate could be found. However, these phenazines were also to serve as the parent compounds for the development of the desired series of phenazines. When it was found that 4-methoxy-o-quinone could not be successfully condensed, under the conditions tried, the phenazines, corresponding to one of the isomers which would have been obtained in each of those condensations, were prepared solely for the purpose of attaining from them the desired series of phenazines.

The main object of this section was therefore to prepare either one of the isomeric nitro-methoxyphenazines possible in each of the four Hinsberg condensations of Section II, or a closely related derivative, in such quantities that a series of related phenazines

could be developed therefrom and by a method which would give a product of known orientation.

Eckert and Steiner[27] found that phenazine could be prepared by the mild oxidative ring closure of o,o'-diaminodiphenylamine. Tomlinson[29] found that almost quantitative yields of methyl- and methoxyphenazines could be prepared from the corresponding o,o'-diaminodiphenylamines by this method and Elderfield et al[9] found that a third amino group ortho to the diphenylamine linkage remained unaffected during the ring closure and prepared 1-aminophenazines in good yield by this method.

It was decided to use this method for the preparation of the desired phenazines. The assumption was made that a third amino group, para to the diphenylamine linkage would remain unaffected and not interfere with the ring closure during the relatively mild conditions under which the ring is closed, when 2-aminophenazines were to be prepared.

This method involves the preparation of an intermediate 2,2'-dinitrodiphenylamine and reduction thereof to the 2,2'-diaminodiphenylamine followed by the oxidative cyclisation.

Diphenylamines are prepared by an Ullman type of condensation. By eliminating hydrogen halide between an aniline and a halobenzene a diphenylamine can be formed. A large number of diphenylamines have been prepared by this method. In this preparation the ease with which the different halogen atoms are eliminated follows the usual pattern, i.e. iodine is more readily lost than bromine and bromine more readily than chlorine. Electron attracting groups, such as the nitro group, especially ortho and para to the halogen atom greatly facilitate the loss of the halogen atom.

Successful condensations of this nature have been accomplished under a variety of conditions. The conditions required for the preparation of a diphenylamine are largely dependent on the reactivity

of the halogen atom.

Fischer[8] obtained 2,4-dinitro-4'-methoxydiphenylamine by refluxing 2,4-dinitrobromobenzene with p-anisidine in alcohol. 2,4-Dinitrodiphenylamine was obtained by heating 2,4-dinitro-chlorobenzene and aniline on a steam bath for 30 minutes. In cases where the halogen atom was less reactive more vigorous conditions and a catalyst were required to effect the condensation. Tomlinson[29] prepared 2,2'-dinitro-4,4'-dimethyldiphenylamine by heating 2-nitro-4-methyl-iodobenzene and 2-nitro-4-methylaniline together at 160° in the presence of copper powder and potassium carbonate. Heating the reactants together in the presence of a weak inorganic base with[25,30,76] or without[38,77,78] a catalyst such as copper bronze or cuprous chloride in the absence of a solvent is a method often employed. This method, however, has the disadvantage that sublimation of the reactants may take place and that complete reaction may not take place if the product has a high melting point and the reaction mixture solidifies.

A method frequently used and one that eliminates the disadvantages of the previous one, is heating aniline and a halo compound together in nitrobenzene, in the presence of copper bronze and an inorganic base such as anhydrous sodium carbonate or anhydrous sodium acetate, at about 210°. By this method Hegedus[30] prepared 2,6,2'-trinitrodiphenylamine from o-iodonitrobenzene and 2,6-dinitroaniline. Elderfield et al[9] found that the addition of a little water to the nitrobenzene increased the yield in some of their preparations.

Yields obtained by these methods varied considerably but were usually about 50%. One case was noticed where there was found to be an optimum length of time of heating and that longer or shorter periods of heating decreased the yield of the diphenylamine[25].

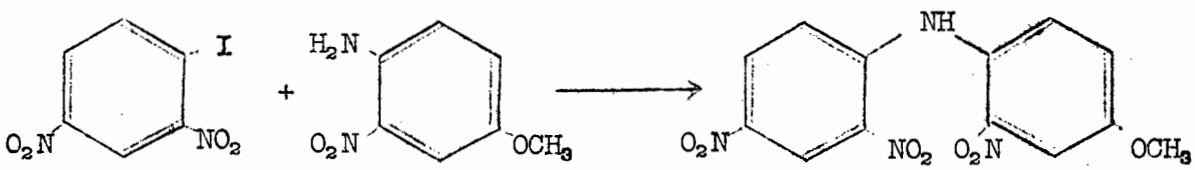
Attempted preparation of 2-amino-7-methoxyphenazine.

2-Amino-7-methoxyphenazine had previously been prepared by Fischer[8] by heating 2,4-diamino-4'-methoxydiphenylamine with lead oxide.

Korner[79] has prepared 2,4-dinitroiodobenzene by the nitration of o-iodonitrobenzene. His method of nitration was used for the preparation of 2,4-dinitroiodobenzene from p-iodonitrobenzene. This method was preferred as there was no possibility of the formation of the 2,6-dinitro isomer.

2,4,2'-Trinitro-4'-methoxydiphenylamine (I) could not be prepared by refluxing 4-methoxy-2-nitroaniline and 2,4-dinitrochlorobenzene in alcohol, or by heating these reagents, or the corresponding iodo-derivative, in the presence of potassium carbonate and copper bronze powder.

The desired condensation was achieved by heating the above reagents in nitrobenzene.



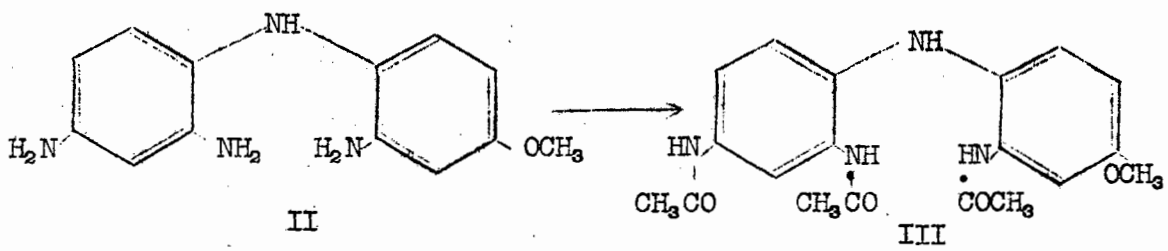
I

A 30 - 35% yield of 2,4,2'-trinitro-4'-methoxydiphenylamine (I) was obtained by heating at 140° for 10 hours and a 10% yield after refluxing for only 30 minutes. As the product obtained by the second method had a decomposed appearance and required a number of recrystallisations to purify and as the first method required practically no attention during the heating period and gave a fairly pure product, no further attention was given to the second method. It was found that the percentage yield decreased slightly with increasing amounts of starting material.

It was interesting to note that a 17% yield of 2,4,2'-trinitro -4'-methoxydiphenylamine was obtained on refluxing with 2,4-dinitrochlorobenzene instead of the corresponding iodo compound (10%).

The method of isolation of the diphenylamines followed by Elderfield et al[9] was preferred above that of removing the nitrobenzene and unchanged reactants by steam distillation. Their method, by which the nitrophenazine and byproducts are removed from the diphenylamine by their greater solubility in alcohol, was very much more rapid than a steam distillation and gave a product of comparable purity in a comparable yield.

2,4,2'-Trinitro-4'-methoxydiphenylamine was hydrogenated to give 2,4,2'-triamino-4'-methoxydiphenylamine (II). This was not isolated in a pure state but immediately acetylated and 2,4,2'-triacetamido-4' -methoxydiphenylamine (III) obtained.



The 2,4,2'-triamino-4'-methoxydiphenylamine (II) could not be ring closed by the oxidative action of ferric chloride in either aqueous-alcoholic or aqueous hydrochloric acid solution. The product isolated by this treatment could not be recrystallised or vacuum sublimed to purify, and did not melt below 360°. As 2-amino-7 -methoxyphenazine has a melting point of 216° - 7°[8] it had evidently not been formed in this reaction.

2,4,2'-Triamino-4'-methoxydiphenylamine was not ring closed in acetic acid either, after removal of the catalyst,by a ferric chloride solution. It was observed on filtering off the Adam's catalyst from the acetic acid solution of 2,4,2'-triamino-4'-methoxydiphenylamine,

that a blue colour developed around the catalyst during the filtration in the presence of air. As the other aminophenazines which had been prepared, (although they were 1-aminophenazines as compared to a 2-aminophenazine possible by this preparation) had been blue in dilute acid, it was thought that this was an indication of the atmospheric oxidation of 2,4,2'-triamino-4'-methoxydiphenylamine to 2-amino-7-methoxyphenazine. However, on bubbling air through an acetic acid solution of 2,4,2'-triamino-4'-methoxydiphenylamine, both in the presence and the absence of the Adam's catalyst, a product similar to that obtained by the previous methods was isolated. This blue colour was later also found to develop in an alcoholic solution of 2,4,2'-triamino-4'-methoxydiphenylamine on exposure to the atmosphere.

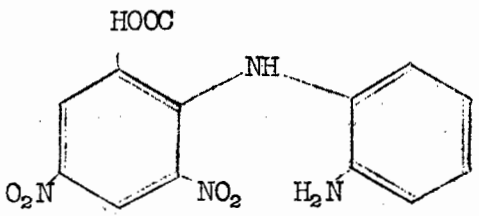
In view of the failure to obtain the desired ring closure by oxidation, attention was diverted to other methods whereby 2,4,2'-triamino-4'-methoxydiphenylamine could be converted to 2-amino-7-methoxyphenazine. A method which presented itself was that whereby 2,2'-diaminodiphenylmethanes are converted to acridans, by heating with acids, usually hydrochloric acid, at temperatures varying between refluxing and 210°. By this method ammonia is eliminated and the ring closed[80]. Similarly Tauber[81] converted 2,2'-diaminodiphenyl (IV) to carbazole (V) quantatively, by heating with sulphuric acid, ammonia being eliminated between the two amino groups.

IV V

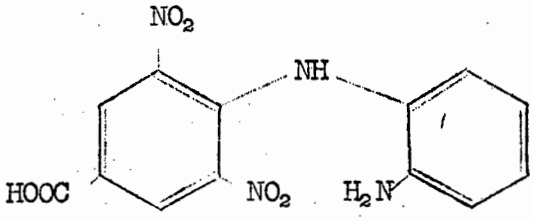
An attempt was made to ring close 2,4,2'-triamino-4'-methoxydiphenylamine by this method. There was the danger in this procedure that the methoxy group could be demethylated and also that the amino

group could be replaced by a hydroxy group. Relatively mild conditions were therefore used in an attempt to achieve the desired ring closure without these side reactions becoming prominent. 2,4,2'-Triamino-4'-methoxydiphenylamine was refluxed with 6 N hydrochloric acid. No product was isolated in sufficient quantity for it to be identified, but the product obtained was soluble in alkali, red in colour and did not melt below 360°, so that it seemed as if 2-amino-7-hydroxyphenazine, which has similar properties[39], might possibly have been formed. After heating 2,4,2'-triamino-4'-methoxydiphenylamine with concentrated hydrochloric acid at 130° - 135° no product could be isolated.

Ullmann[31] by heating 2,4-dinitro-2'-aminodiphenylamine-6-carboxylic acid (VI) with stannous chloride and hydrochloric acid successfully reduced, decarboxylated and ring closed this compound to obtain 2-aminophenazine.

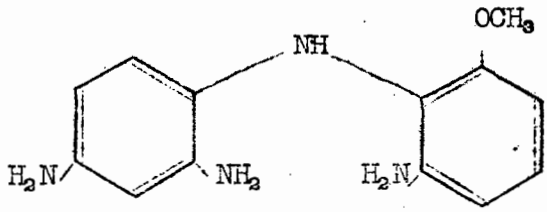


VI



VII

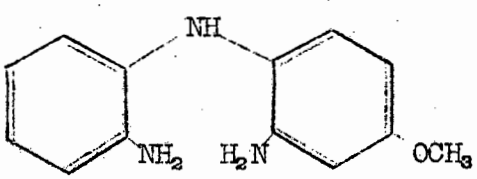
Albert and Duewell[32] similarly reduced, decarboxylated and ring closed 2,6-dinitro-2'-aminodiphenylamine-4-carboxylic acid (VII) to obtain 1-aminophenazine. An unsuccessful attempt to prepare 2-amino-7-methoxyphenazine and/or 2-amino-7-hydroxyphenazine by reduction and ring closure of 2,4,2'-trinitro-4'-methoxydiphenylamine with stannous chloride and hydrochloric acid at 110° - 130° was made. Albert and Duewell[32] found, in their preparation of 1-aminophenazine, that if too low a temperature was used no ring closure took place. However, as on trying this method of cyclisation on 2,4,2'-triamino-6'-methoxydiphenylamine (VIII) at 170°, no cyclisation was achieved, it was considered unlikely that elevated temperatures would be any more successful with this compound.



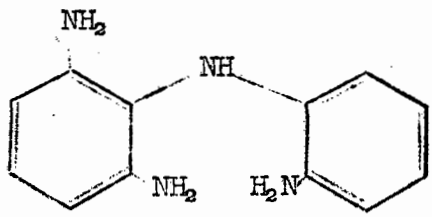
VIII

Rozum[82] prepared a number of methyl- and methoxyphenazines by adding sodium to a methanol suspension of the 2,2'-dinitrodiphenylamines and heating. An unsuccessful attempt to use this method, as described in the American Chemical Abstracts[83], for the preparation of 2-amino -7-methoxyphenazine was made.

2-Methoxyphenazine was prepared from 2,2'-diamino-4-methoxydiphenylamine (IX) and 1-aminophenazine from 2,2',6-triaminodiphenylamines (X) by ferric chloride oxidation in hydrochloric acid medium.



IX

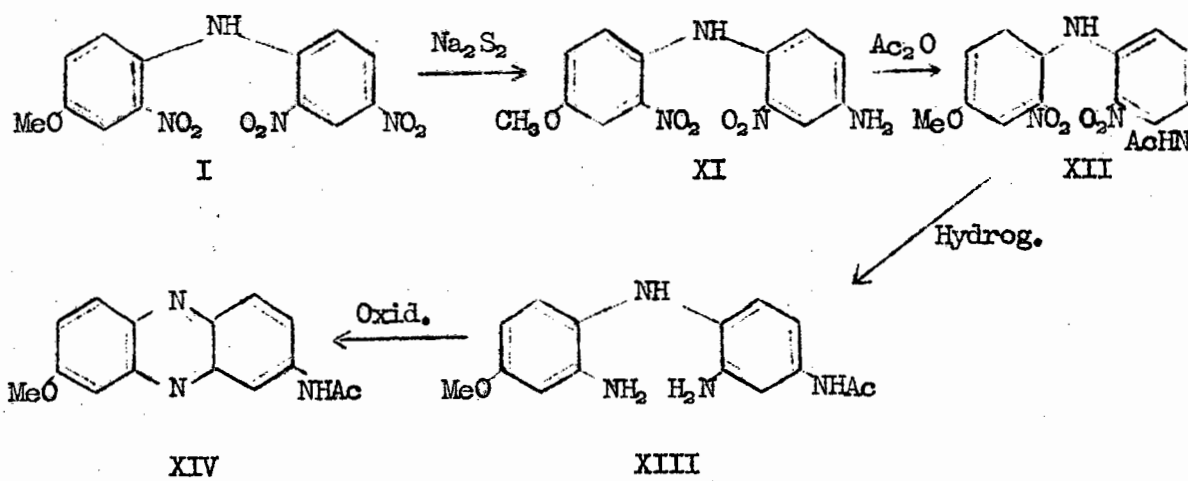


X

The failure of this method to work with 2,4,2'-triamino-4'-methoxydiphenylamine (II) would therefore appear to be due to the presence of the third amino group para to the diphenylamine linkage. If this group should be more readily oxidised than the amino group ortho to the diphenylamine linkage on the same phenyl nucleus, ring closure, which irrespective of the mechanism must involve at some stage oxidation of the o-amino group, will be inhibited. The resulting p-quinoid type of structure will make the molecule readily susceptible

to oxidative decomposition. If this is the case, then, oxidative decomposition of the molecule could account for the failure of this method, as well as of the other methods attempted.

Assuming this argument to be correct the answer to the problem would be protection of the 4-amino group. With this object in view the following method was embarked upon: It has been found that generally a nitro group with no substituents in a position ortho to it is more readily reduced than a nitro group with an ortho substituent. It was hoped that by the treatment of 2,4,2'-trinitro-4'-methoxydiphenylamine (I) with the theoretical amount of sodium polysulphide required for the reduction of one nitro group, the 4-nitro group alone would be reduced, providing the above generalisation holds for this compound. The mono amino (XI) compound would then be acetylated and reduction of 2,2'-dinitro-4-acetamido-4'-methoxydiphenylamine (XII) followed by oxidation of the resultant 2,2'-diamino-4-acetamido-4'-methoxydiphenylamine (XIII) would then give 2-acetamido-7-methoxyphenazine (XIV).



I XI XII

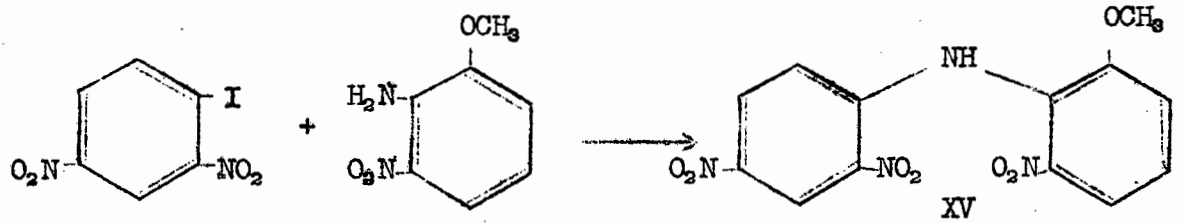
XIV XIII

This would only be successful if the acetamido group was not hydrolysed in the dilute hydrochloric acid solution, or if the ring closure occurred before hydrolysis of the acetamido group took place.

The desired reduction could, however not be accomplished.

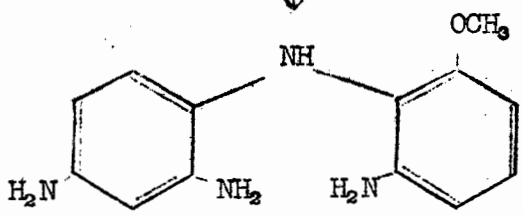
Attempted preparation of 1-methoxy-6-aminophenazine.

The intermediate 2,4,2'-trinitro-6'-methoxydiphenylamine (XV) required for this preparation was prepared by refluxing 2,4-dinitroiodobenzene and 3-nitro-o-anisidine (XVI), prepared by the method of Lane and Williams[84], in nitrobenzene with copper bronze powder and potassium carbonate.



XVI

XV

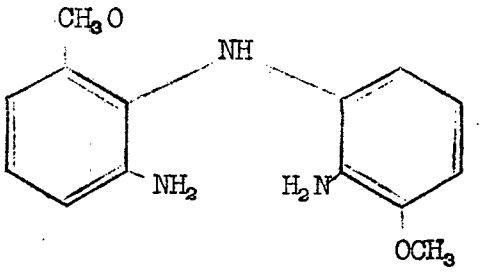


VIII

This product was hydrogenated in absolute alcohol in the presence of Adam's catalyst to give 2,4,2'-triamino-6'-methoxydiphenylamine (VIII), but as this compound appeared to be unstable when exposed to the atmosphere, no attempt was made to isolate it. That it had been obtained was proved by acetylating the crude compound immediately with acetic anhydride at room temperature when 2,4,2'-triacetamido-6'-methoxydiphenylamine was obtained.

On treating an aqueous-alcoholic hydrochloric acid solution of 2,4,2'-triamino-6'-methoxydiphenylamine with a ferric chloride solution a product which could not be vacuum sublimed or recrystallised and did not melt below 360° was obtained. Clemo and Daglish[26] prepared

1,5-dimethoxyphenazine by the oxidation of 2,2'-diamino-6,3'-dimethoxydiphenylamine (XVII) with ferric chloride in hydrochloric acid.



XVII

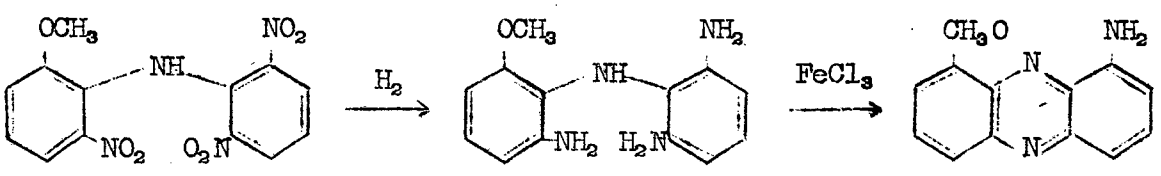
The failure to obtain 1-methoxy-6-aminophenazine from 2,4,2'-triamino -6'-methoxydiphenylamine by this method is thus apparently again due to the presence of the amino group para to the diphenylamine linkage, as a methoxy group in a position ortho to this linkage, from the result of Clemo and Daglish[25], does not prevent successful ring closure.

No ring closure could be effected by refluxing 2,4,2'-triamino -6'-methoxydiphenylamine with concentrated hydrochloric acid. On attempting ring closure at higher temperatures, by heating in a sealed tube with 25% sulphuric acid at 170°, no product was isolated either.

2,4,2'-Triamino-6'-methoxydiphenylamine could not be ring closed by heating dry with cuprous chloride.

Attempted preparation of 2,6,2'-trinitro-6'-methoxydiphenylamine.

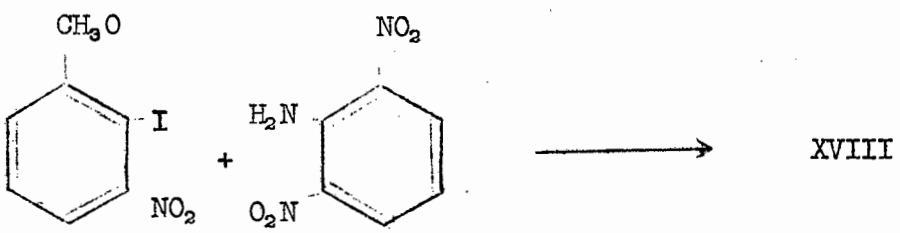
The preparation of 2,6,2'-trinitro-6'-methoxydiphenylamine (XVIII) was to have been the first step in the synthesis of 1-amino-8-methoxyphenazine (XIX) by the ferric chloride oxidation of 2,6,2'-triamino -6'-methoxydiphenylamine (XX).



XVIII XX XIX

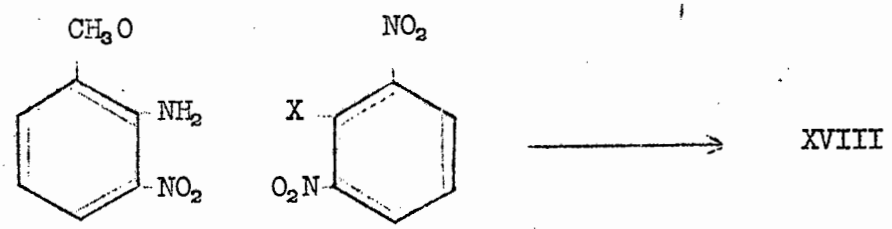
There were two methods by which this diphenylamine could apparently be prepared. The first was condensation of 3-nitro-2-haloanisole (XXI) and 2,6-dinitroaniline, and the second condensation of 3-nitro-o-anisidine (XVI) and 2,6-dinitrohalobenzene (XXII).

(i)



XXI

(ii)



XVI XXII

An attempt was made to prepare 2-iodo-3-nitrophenol, by the method of Datta and Prosad[85], from which 2-iodo-3-nitroanisole was to be prepared by methylation. On iodination of m-nitrophenol in ammonia solution a product of melting point 138° - 142° was obtained. Datta and Prosad claimed a melting point of 134° for their product. The melting point of 6-iodo-3-nitrophenol is given as 146° - 147°[86]. From the melting point of the product obtained it would appear that there is also 6-iodo-3 -nitrophenol present. Steric considerations make it the most probable of the two isomers to have formed. Due to this uncertainty about the product the second approach was attempted instead.

An attempt was made to prepare 2,6-dinitrochlorobenzene and separate it from 2,4-dinitrochlorobenzene after nitration of o-chlorobenzene by the method of Borsche and Rantscheff[87]. Neither by their method nor by chromatography on alumina, with petroleum ether as eluant,

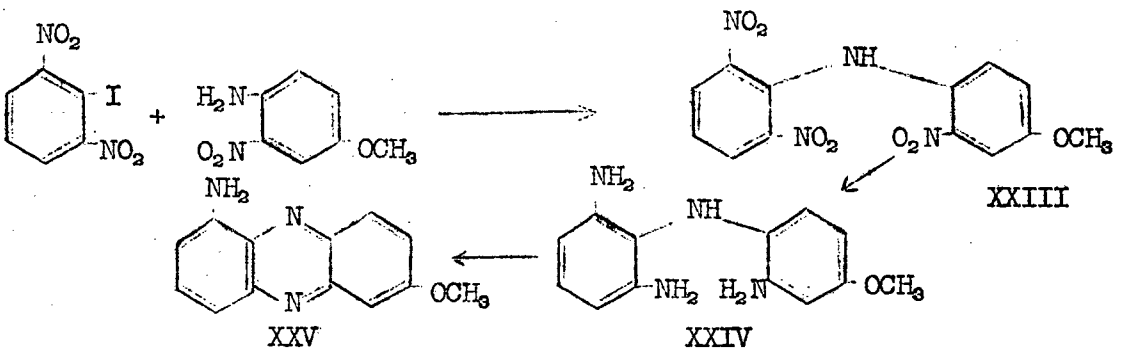
was 2,6-dinitrochlorobenzene isolated.

2,6-Dinitroiodobenzene was prepared by diazotisation and a Sandmeyer reaction from 2,6-dinitroaniline[88]. The 2,6-dinitroaniline was obtained from o-chloronitrobenzene by a combination of the method of Rabinowitz and Wagner[73] and the method of Schultz[89]. By sulphonation and nitration, followed by replacement of the chlorine atom by an amino group, in that order o-chloronitrobenzene was converted to the potassium salt of 4-amino-3,5-dinitrobenzene-sulphonic acid by the method of Rabinowitz and Wagner[73]. The method of desulphonation of Schultz[89] was followed, being much more rapid than that of Rabinowitz and Wagner and giving a comparable yield.

Condensations of 2,6-dinitro-iodobenzene and 3-nitro-o-anisidine were attempted under a variety of conditions. In no case was the condensation successfully accomplished. Steric hindrance might be advanced as a reason for not being able to accomplish this condensation. A similar observation was made by Clemo and Daglish[90]. They failed to condense a number of compounds with the halogen atom or the amino group similarly situated. Amongst these was 2-chloro-3-nitroanisole and 3-nitro-2-aminoanisole.

Preparation of 1-amino-6-methoxyphenazine and derivatives.

2,6,2'-Trinitro-4'-methoxydiphenylamine (XXIII) was prepared by heating 2,6-dinitro-iodobenzene and 4-methoxy-o-nitroaniline in nitrobenzene with copper bronze powder and potassium carbonate at 120° - 130° for 12 hours.



The 2,6,2'-trinitro-4'-methoxydiphenylamine was hydrogenated in alcohol in the presence of Adam's catalyst. After the catalyst had been filtered off, an aqueous-alcoholic hydrochloric acid solution of the 2,6,2'-triamino-4'-methoxydiphenylamine (XXIV) was treated with a ferric chloride solution. Blue green crystals of what is apparently the hydrochloride of 1-amino-6-methoxyphenazine soon separated. By neutralisation of the aqueous solution, 1-amino-6-methoxyphenazine (XXV) was obtained in a 75% yield. This yield could be slightly increased by removal of all the alcohol from the 2,6,2'-triamino-4'-methoxydiphenylamine and effecting the ring closure by the ferric chloride oxidation in dilute aqueous hydrochloric acid solution.

1-Amino-6-methoxyphenazine was acetylated at room temperature by acetic anhydride to give 1-acetamido-6-methoxyphenazine.

Demethylation of 1-amino-6-methoxyphenazine was effected by refluxing with 48% hydrobromic acid. 1-Amino-6-hydroxyphenazine could also be obtained from it, although in very much smaller yield, by heating with concentrated hydrochloric acid.

On treating 1-amino-6-hydroxyphenazine with acetic anhydride at room temperature only the amino group was acetylated and 1-acetamido-6-hydroxyphenazine formed.

On the other hand, by a Chattaway type of acetylation of 1-amino-6-hydroxyphenazine, only the hydroxy group was acetylated and thus 1-amino-6-acetoxyphenazine obtained.

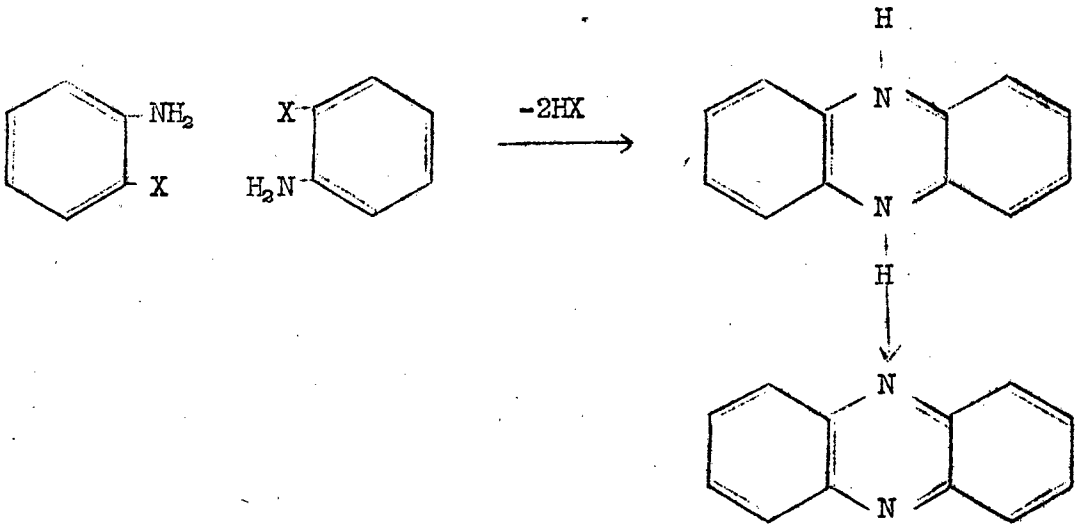
1-Acetamido-6-acetoxyphenazine was obtained by refluxing 1-amino-6-hydroxyphenazine with acetic anhydride and fused sodium acetate, both groups were acetylated.

1,6-Dihydroxyphenazine was prepared from 1-amino-6-hydroxyphenazine by heating with 3 N sulphuric acid under pressure at 150°. On heating this product it was found to decompose at 303° in a sealed tube. This was found to agree with the result of Serebryanyi[43] who reported

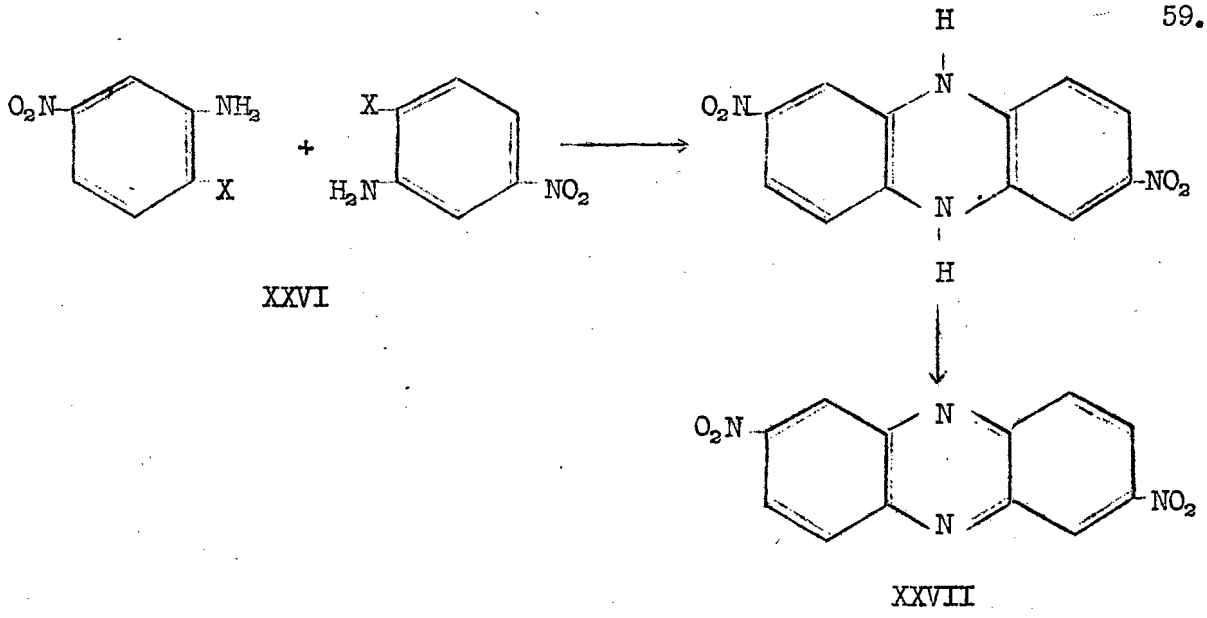
1,6-dihydroxyphenazine as decomposing at 305° - 6° in a sealed tube. Although no analysis was done on this product, this agreement in behaviour on heating was taken as sufficient evidence that 1,6-dihydroxyphenazine had been formed.

Attempted preparation of 2,6-dinitrophenazine.

It was decided to attempt a novel preparation of 2,6-dinitrophenazine. If by the elimination of one molecule of hydrogen halide between an amino group on one molecule and a halogen atom on another, a diphenylamine linkage could be formed, no reason could be seen why, by the elimination of 2 molecules of hydrogen halide, from two molecules, each having an amino group ortho to a halide group, a dihydrophenazine, and thus a phenazine should not be formed.



With a nitro group para to the halogen it was hoped the halogen in o-halo-aniline would be active enough to take part in such a condensation and thus 2-halo-5-nitroaniline (XXVI) would autocondense and give 2,6-dinitrophenazine (XXVII) by the following scheme.



XXVI

XXVII

2-Chloro-5-nitroaniline was prepared by the method of Buchanan and Graham[80].

The usual methods by which diphenylamines were prepared were tried in an attempt to autocondense the 2-chloro-5-nitroaniline. It was refluxed with copper bronze powder and sodium acetate or potassium carbonate in nitrobenzene for varying lengths of time. On refluxing for 30 minutes no condensation took place and on refluxing for 9 hours no product could be isolated. On heating in the absence of a solvent sublimation of the 2-chloro-5-nitroaniline took place and no condensation product was obtained. Heating in a sealed tube at elevated temperatures resulted in violent explosions. These explosions might have been caused by condensation taking place and the liberated acid then reacting with the potassium carbonate to give carbon dioxide or with the sodium acetate to give acetic acid, or by decomposition of the 2-chloro-5-nitroaniline.

As condensations with the 2-chloro-5-nitroaniline were not successful it was thought that by preparing the corresponding bromo or iodo compound, the greater reactivity of these halogen groups might result in condensation taking place.

Due to the ease with which 2-chloro-5-nitroaniline had been

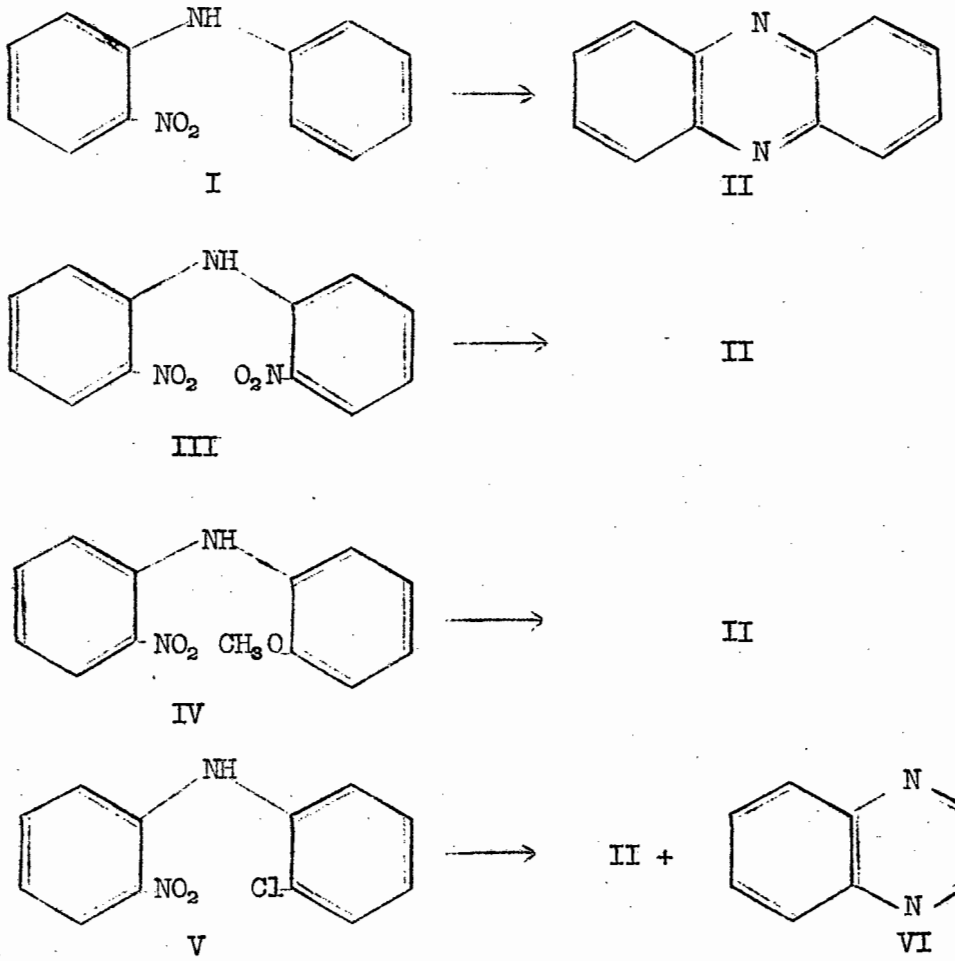
obtained by the method of Graham and Buchanan it was decided to try and prepare the corresponding bromo compound by a similar method. This was readily achieved. o-Bromoaniline and phthalic anhydride were fused together to give N-(o-bromophenyl)-phthalimide. Nitration of this product gave N-(2-bromo-5-nitrophenyl)-phthalimide from which 2-bromo -5-nitroaniline was obtained by alkaline hydrolysis.

2-Bromo-5-nitroaniline behaved similarly to the chloro compound on attempting condensations.

SECTION IIIB.

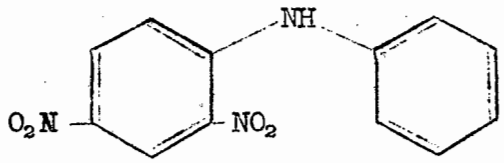
No nitrophenazines have as yet been prepared by Vivian's method from a 2-nitrodiphenylamine by heating with an "oxygen acceptor" such as metallic iron or ferrous oxalate and lead. It was decided to try this method for the preparation of a nitrophenazine and if it had possibilities, to try and develop it in an attempt to prepare those phenazines it had not been possible to prepare by the Hinsberg condensations in Section II, or by the ferric chloride oxidations of the 2,2'-diaminodiphenylamines of Section IIIA.

The method of Vivian has the drawback that substituents in the 2' position in a 2-nitrodiphenylamine are usually eliminated in preference to a hydrogen atom ortho to the diphenylamine linkage and the ring then closed in that position[35,37]. Thus on heating 2-nitrodiphenylamine (I) with iron, phenazine (II) is formed. Phenazine is, however, also formed on heating 2,2'-dinitrodiphenylamine (III) and 2-nitro-2'-methoxydiphenylamine (IV) with iron. On heating 2-nitro-2' -chlorodiphenylamine (V) with lead and ferrous oxalate both 1-chlorophenazine (VI) and phenazine were formed[71].



It has also been found by Vivian et al[38] that in this reductive ring closure of nitro compounds in the preparation of alkoxyphenazines, isomers may be formed where the possibility exists. These factors have a limiting influence on the preparation of nitro-methoxyphenazines by this method.

An attempt was first made to ring close 2,4-dinitrodiphenylamine (VII) by this method.



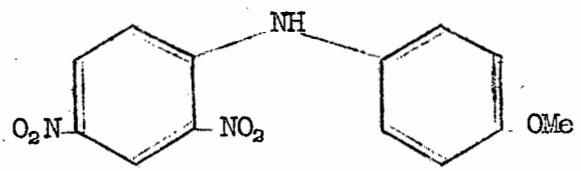
VII

Waterman and Vivian[35] found that the additional nitro group of 2,4-dinitrophenylamine and of 2,4-dinitro-4'-hydroxydiphenylamine rendered the reaction so violent that no product could be isolated.

On heating 2,4-dinitrodiphenylamine with lead and ferrous oxalate a vigorous reaction took place. A strong isocyanide type of smell was noticed in the reaction mixture.

By chromatography of the product of the reaction on alumina, using benzene as eluting solvent, four bands were found to develop. By elution of these bands a small amount of what is apparently 2-nitrophenazine was isolated.

One of the bands on elution and evaporation of the benzene gave a reddish product with the same colour reactions in acid as 2-aminophenazine. This product behaved identically to 2-aminophenazine on paper chromatograms. Apparently 2-aminophenazine had been formed in this reaction. Apart from unchanged 2,4-dinitrodiphenylamine none of the other products could be identified.



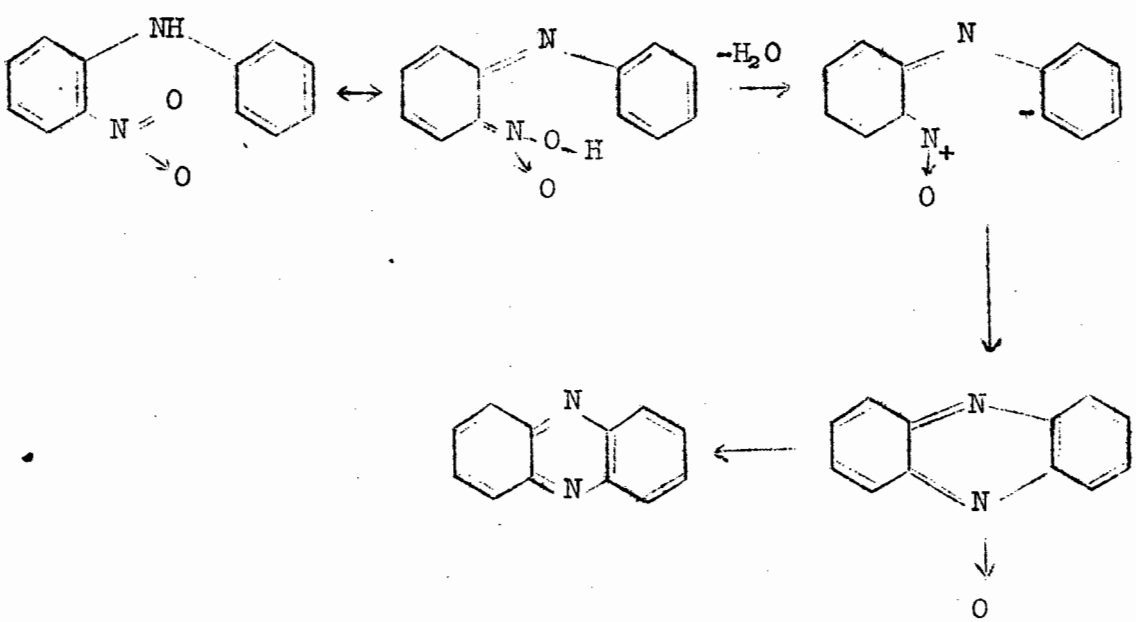
VIII

2,4-Dinitro-4'-methoxydiphenylamine (VIII) was heated with lead and ferrous oxalate. After separation of unchanged starting material the product of the reaction was chromatographed on alumina with benzene as eluting solvent. A number of bands developed, the most prominent being a purple band. The residue, after elution and evaporation of this band behaved identically to 2-aminophenazine, in acid and on paper chromatograms.

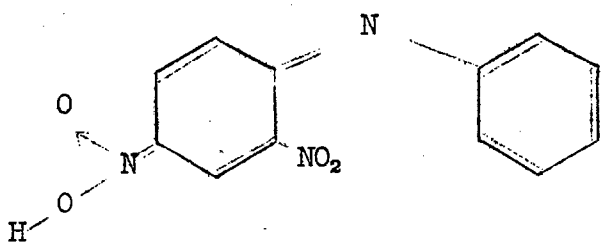
Both on heating 2,4-dinitrodiphenylamine and 2,4-dinitro-4'-methoxydiphenylamine, 2-aminophenazine is apparently one of the

products. In the case of the attempted reductive ring closure of 2,4-dinitro-4'-methoxydiphenylamine not only is the nitro group reduced to an amino group but demethoxylation appears to take place as well.

A suggested mechanism for this ring closure is the following:

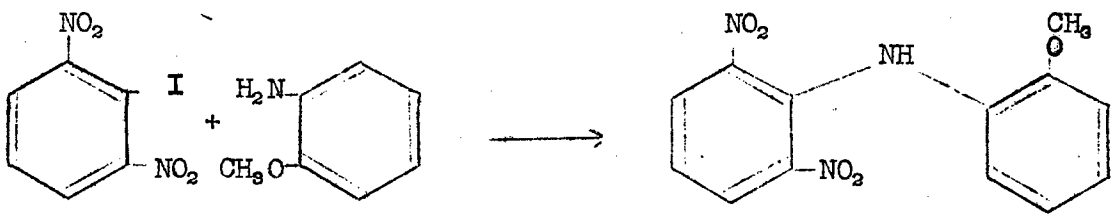


If such a mechanism is followed, the presence of a second nitro group, para to the diphenylamine linkage may well inhibit the reaction, due to the following possible structure.



Attempted preparation of 1-nitro-8-methoxyphenazine.

As the intermediate 2,6,2'-trinitro-6'-methoxyphenylamine, required for the preparation of 1-amino-8-methoxyphenazine from the corresponding triamine by ferric chloride oxidation, could not be prepared and as the method of Vivian did not seem promising for such a preparation, a new approach to this product was sought. It was decided to attempt the ring closure of 2-amino-6-nitro-2'-methoxydiphenylamine by heating with lead dioxide, hoping that perhaps the methoxy group would not be eliminated.



2-6-Dinitro-2'-methoxydiphenylamine was prepared by refluxing 2,6-dinitroiodobenzene and o-anisidine in alcohol.

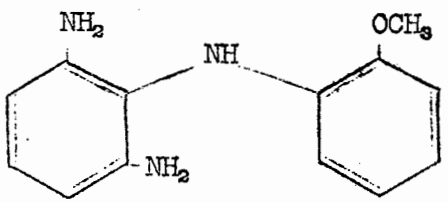
A reduction of only one of the nitro groups of 2,6-dinitro-2'-methoxydiphenylamine by adding the calculated amount of sodium polysulphide could not be accomplished. On treating 2,6-dinitro-2'-methoxydiphenylamine with sufficient stannous chloride and hydrochloric acid for the reduction of only one nitro group, 2,6-diamino-2'-methoxydiphenylamine and unchanged 2,6-dinitro-2'-methoxydiphenylamine were recovered from the reaction mixture.

2,6-Diamino-2'-methoxydiphenylamine was prepared by the hydrogenation of 2,6-dinitro-2'-methoxydiphenylamine in absolute alcohol in the presence of palladium charcoal catalyst. Vigorous decompositions took place on heating 2,6-diamino-2'-methoxydiphenylamine with lead dioxide.

SECTION IV.

A new approach to phenazine synthesis.

[A] Due to the violence of the reaction on heating 2,6-diamino-2'-methoxydiphenylamine (I) with lead dioxide, a method was sought whereby the reaction could be modified. Heating the reagents



I

together in a high boiling, inert solvent was a method which presented itself as possibly being able to modify the reaction yet being vigorous enough for ring closure to take place.

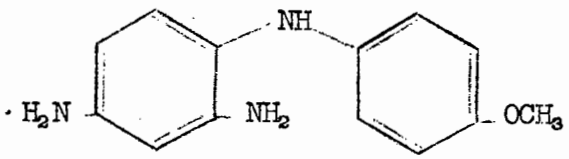
A solution of 2,6-diamino-2'-methoxydiphenylamine in xylene was refluxed with powdered lead dioxide for 1 hour. The lead dioxide was filtered off and the xylene solution then either extracted with hydrochloric acid to remove the phenazine or the xylene solution acidified and the xylene removed by steam distillation. By neutralisation of the acid solution 1-aminophenazine was precipitated. A 43% yield of 1-aminophenazine was obtained. Due to the simplicity of this method, the ease with which the 1-aminophenazine is isolated and the good yield, this method must be regarded as one of the best whereby 1-aminophenazine may be prepared. A further salient feature is the relative ease whereby the starting materials may be obtained.

The observation of McCombie et al[34], that a methoxy group ortho to the diphenylamine linkage is eliminated in preference to a hydrogen atom ortho to the linkage during the oxidative ring closure of 2-amino-2'-methoxydiphenylamine with powdered lead dioxide in the absence of a solvent was found to hold in solution as well.

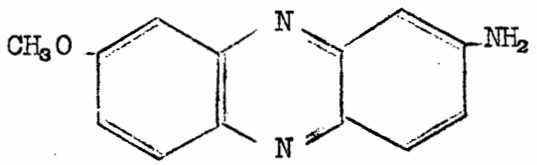
This modified method of Fischer was applied in the preparation of other phenazines. A small yield of 2-aminophenazine was prepared by this method from both 2,4'- and 2,4-diaminodiphenylamine.

2,2'-Diaminodiphenylamine was treated by this method. 1-Aminophenazine was obtained in a yield so small that its presence was only detected on paper chromatograms. Rather unexpectedly no phenazine could definitely be identified in the product isolated. As phenazine was obtained on the reductive ring closure of 2,2'-dinitrodiphenylamine by Vivian's method[35] and as this method is so closely related to Vivian's method, phenazine was expected as a product. Phenazine was also expected in view of the fact that phenazine is formed by the oxidative action of ferric chloride on 2,2'-diaminodiphenylamine.

2-Aminodiphenylamine was converted to phenazine, in small yield, by this method and 2,4-diamino-4'-methoxydiphenylamine (II) to 2-amino-7-methoxyphenazine (III), also in small yield.



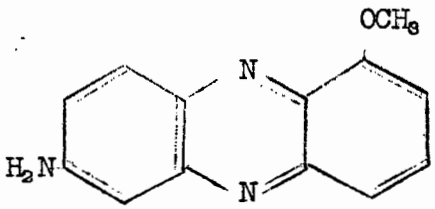
II



III

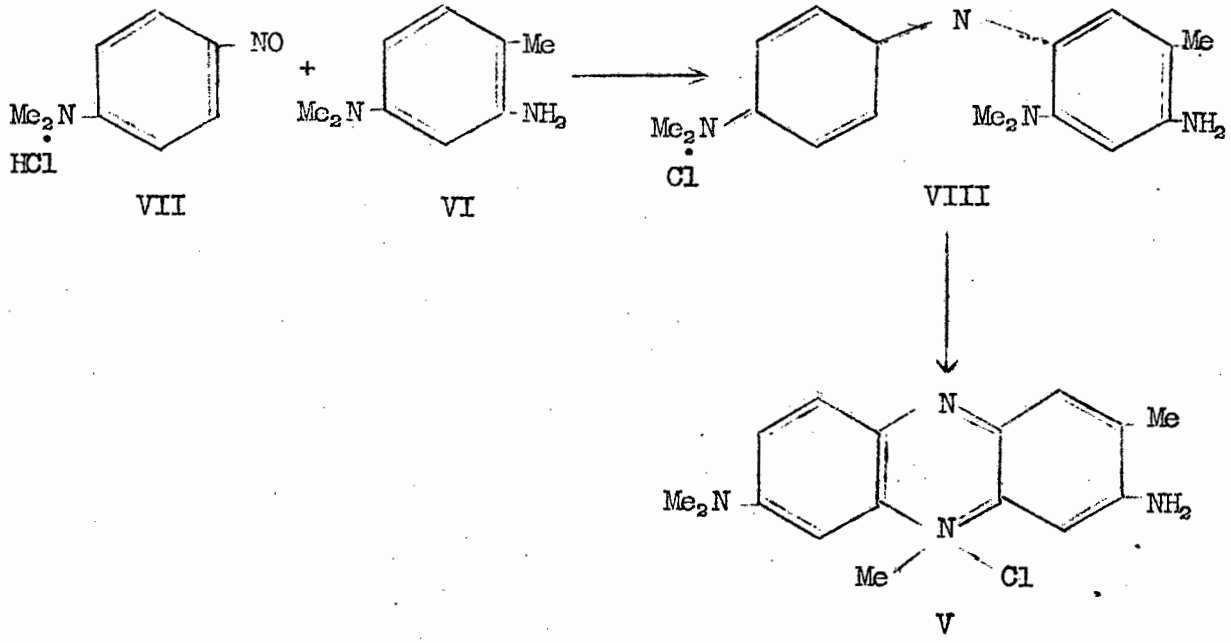
Apart from the preparation of 1-aminophenazine this method has no particular appeal as a synthetic route to phenazines in its present state of development.

[B] Due to the failure of the other methods tried for the preparation of 1-methoxy-6-aminophenazine (IV) a new approach for the synthesis of this compound was tried.



IV

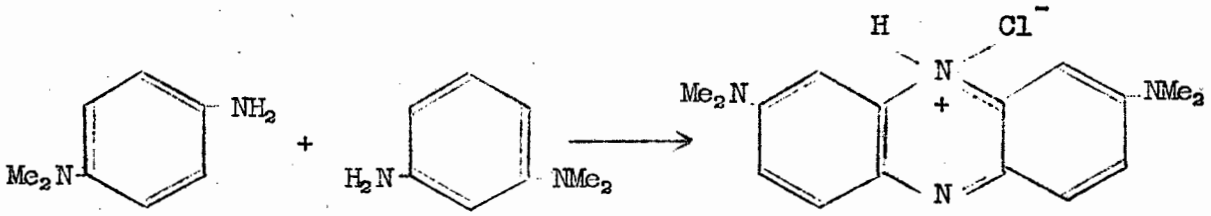
The synthesis of a number of relatively more complex phenazines, with an amino group in a 2 position, are assumed to pass through an intermediate indamine, which has in some cases been stable enough to be isolated and identified[40]. Cohen and Crabtree[40] prepared 2-methyl -3-amino-7-dimethylaminophenazinium methochloride (V) from 2-amino-dimethyl-p-toluidine (VI) and p-nitroso dimethylaniline hydrochloride (VII) by warming the intermediate indamine (VIII), obtained from these reagents in 50% acetic acid.



No reason could be seen why conversion of 2,4'-diamino-6-methoxydiphenylamine (IX) to the intermediate indamine (X) by oxidation, followed by ring closure by heating, should not give 1-methoxy-6-aminophenazine.

2,4'-Dinitro-6-methoxydiphenylamine was prepared by heating p-nitroiodobenzene and 3-nitro-o-anisidine in the presence of copper bronze and potassium carbonate. By hydrogenation in absolute alcohol in the presence of palladium-charcoal catalyst 2,4'-diamino-6-methoxydiphenylamine was obtained as a tar which was not readily solidified. No attempt was made to isolate the 2,4'-diamino-6-methoxydiphenylamine in a pure state as it appeared to decompose on exposure to the atmosphere. Its existence was proved by acetylation when 2,4'-diacetamido-6-methoxydiphenylamine was obtained.

Karrer[92] effected the following conversion,



by heating the reagents together with potassium dichromate and hydrochloric acid, the reaction evidently passing through an intermediate indamine.

An attempt to oxidise 2,4'-diamino-6-methoxydiphenylamine to the indamine by potassium dichromate in dilute sulphuric acid and to effect the ring closure in this medium was made. Due to apparent decomposition under these conditions no product could be isolated.

As it was thought that these oxidising conditions were too vigorous, milder conditions were attempted. As quinones and quinone imines were derived from the corresponding dihydroxy and diamino compounds by oxidation with silver oxide in an inert solvent[93] this method was tried.

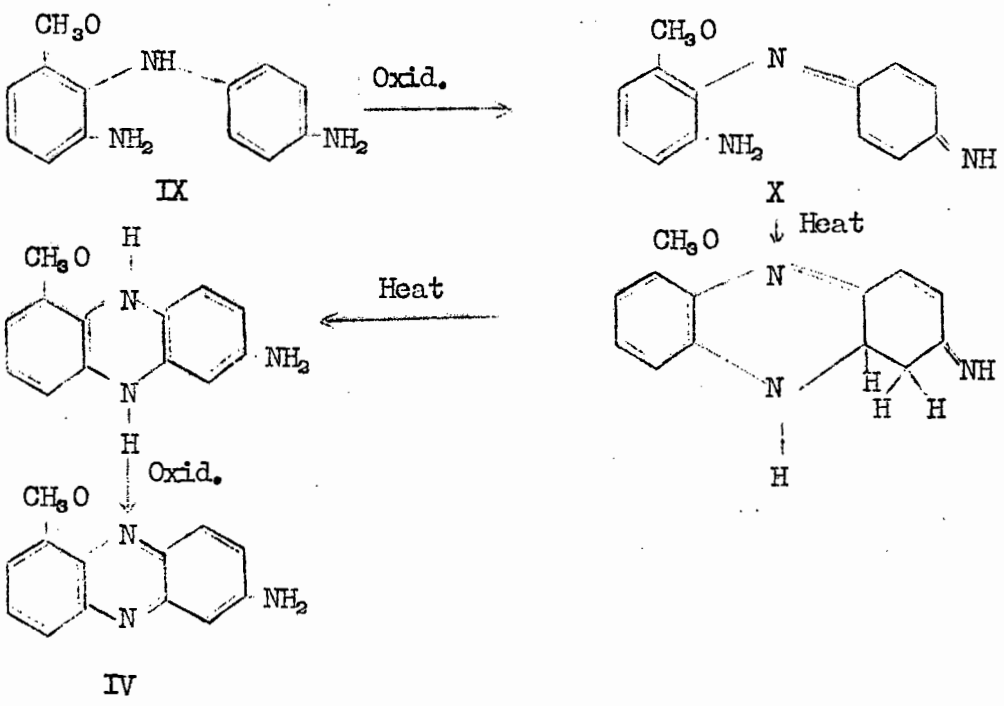
No product could be isolated after shaking 2,4'-diamino-6-methoxydiphenylamine with silver oxide in ether followed by heating in dilute hydrochloric acid.

The failure of these methods led to a search for a mild oxidising agent which would oxidise the 2,4'-diamino-6-methoxydiphenylamine to the intermediate indamine at high temperatures where ring closure would be effected. Heating with a high boiling, oxidative organic solvent was a method which presented itself. Nitrobenzene seemed a possibility as it combined both the desired requirements at its boiling point. Weinmayr[94] prepared carbazole by heating o-aminodiphenyl and an organic nitro substituted compound such as m-dinitrobenzene at 250° - 360° for several hours. Although this is a different type of ring closure, since it is onto a benzene ring containing no substituents, the success of this method did lend encouragement to this approach.

2,4'-Diamino-6-methoxydiphenylamine (IX) was refluxed in nitrobenzene in the presence of a little m-dinitrobenzene for 5 hours, the solution acidified and the nitrobenzene removed by steam distillation.

By neutralisation of the acid residue 1-methoxy-6-aminophenazine (IV) was obtained in good yield.

A possible mechanism for this ring closure could be:



After the initial success of this method and the ease whereby the product was isolated further preparations by this method were tried.

In all the subsequent cases, first the corresponding nitro-diphenylamines were prepared. This was followed by hydrogenation of these compounds in absolute alcohol in the presence of palladium charcoal. Without removal of the catalyst, the alcohol was evaporated under nitrogen, as these diphenylamines appeared to be unstable, and then immediately refluxed in nitrobenzene solution in the presence of a little m-dinitrobenzene.

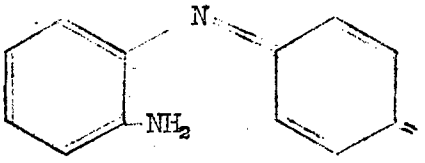
The aim of these preparations was to see if a mechanism of the type suggested was indeed involved in this ring closure and whether eliminations of other groups, such as observed in the ring closure

of similar compounds by the methods of Fischer and Vivian, would take place in this method of ring closure also.

The results obtained are tabulated below.

Starting material	Product	Yield
2,4'-Diamino-6-methoxydiphenylamine	1-methoxy-6-aminophenazine	40%
2,4'-Diaminodiphenylamine	2-aminophenazine	70%
2,4-Diaminodiphenylamine	2-aminophenazine	5%
2,4-Diamino-4'-methoxydiphenylamine	2-amino-7-methoxyphenazine	64%
2-Aminodiphenylamine	Phenazine	Very small
2,2'-Diaminodiphenylamine	1-aminophenazine	50%
2,6-Diamino-2'-methoxydiphenylamine	1-aminophenazine	Small

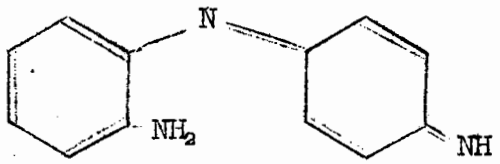
These results seem to indicate that this ring closure does proceed mainly via an intermediate indamine. In all those compounds where the following structure (XI) could arise by oxidation, good yields were recorded.



XI

In cases where that intermediate was not possible the yields were poor. A good example of this was the preparation of 2-aminophenazine from 2,4'-diaminodiphenylamine and from 2,4-diaminophenazine. In the first case the 2,4'-diaminophenazine may be oxidised to the following

indamine (XII).



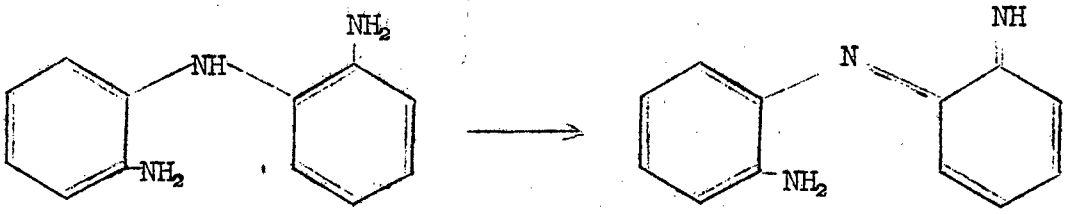
XII

A 70% yield of 2-aminophenazine was obtained. With 2,4-diaminophenazine no such intermediate type of indamine was possible. Only a 5% yield of 2-aminophenazine was obtained. In this case, as in the ring closure of 2-aminodiphenylamine to give phenazine, a similar ring closure to that of Weinmayr[94] in preparing carbazole from o-aminodiphenyl must take place. The phenazine obtained from 2-aminodiphenylamine could only be identified by paper chromatography. If this mechanism is applicable, then in the synthesis of 2-amino-7-methoxyphenazine (III) from 2,4-diamino-4'-methoxydiphenylamine the following is possibly the intermediate (XIII) on the basis of the good yield obtained and the suggested mechanism.

XIII

An interesting observation is the following. 2,2'-Dinitrodiphenylamine on heating with an oxygen acceptor gives phenazine - the one nitro group being eliminated. On heating 2,2'-diaminodiphenylamine with nitrobenzene and a little m-dinitrobenzene, 1-aminophenazine was obtained. There was no elimination of the 2' amino group and ring closure in that position.

The good yield of 1-aminophenazine obtained from 2,2'-diaminophenazine (XIV) seems to indicate the mechanism suggested also applies when a ortho quinone imine type of structure (XV) for the indamine is possible in the intermediate step.



XIV XV

The preparation of 1-aminophenazine as described above, would seem to be one of the best methods for its synthesis.

On treating 2,6-diamino-2-methoxydiphenylamine by this procedure, 1-aminophenazine was obtained in extremely small yield. It could only be identified by paper chromatography. None of the other products could be identified. It would therefore appear that in this method of ring closure a methoxy group ortho to the diphenylamine linkage is eliminated in preference to a hydrogen atom ortho to that linkage, just as was observed in Fischer's method on heating similar compounds with lead dioxide. A similar type of observation was made with Vivian's method on heating a 2-nitrodiphenylamine with an oxygen acceptor.

SECTION V.

Constitution and colour of these phenazines.

Special note was taken of the colour of these compounds, their colour reactions in acid and their fluorescence, for comparison with those of pigments A and B. The absorption of these phenazines was determined in 96% alcoholic solution, in the range 220 - 600 mμ with a Beckman Model D. U. Quartz Spectrophotometer, with quartz cells.

The alcohol used as solvent was purified by refluxing with aluminium powder and potassium hydroxide for approximately 6 hours and the alcohol then distilled from the mixture. Only the middle 80% fraction distilled was collected and used. The alcohol was stored in a ground-glass stoppered bottle.

A table follows indicating the wavelength of maxima of absorption (λ_{max}) and the logarithm of the molecular extinction coefficient ($\log_{10}\varepsilon$) at those wavelengths for these phenazines.

	A		B		C				D	
	λ_{max}	log ε	λ_{max}	log ε	λ_{max}	log ε	λ_{max}	log ε	λ_{max}	log ε
Phenazine			250	±4.1	370	±3.15				
1-Hydroxyphenazine			265	4.712	368	3.485			428	3.336
1-Methoxyphenazine			260	4.743	360	3.872			402	3.436
1-Acetoxyphenazine			251	4.980	362	4.061				
1-Methoxy-4-nitrophenazine			258	4.760	360	4.047			402	3.729
1-Acetoxy-4-nitrophenazine			252	4.752	365	4.119			510	2.233
1,4-Dihydroxyphenazine	240	4.309	285	4.589	358	3.443	375	3.434	488	3.115
1,4-Diacetoxyphenazine			255	4.902	365	4.049				
1-Acetoxy-4-aminophenazine	240	4.449	290	4.522	360	3.559	375	3.571	498	3.357
1-Acetoxy-4-acetamidophenazine	250	4.539	265	4.579	368	3.963			430	3.544
1-Aminophenazine			290	4.541	365	3.600	372	3.640	500	3.293
1-Aminophenazine in N/10 HCl			250	4.801	302	4.169			368	3.997
1-Acetamidophenazine			262	4.699	360	3.940			412	3.542
1-Methylaminophenazine	242	4.521	298	4.566	360	3.484	372	3.535	518	3.415
1-Amino-4-nitrophenazine	240	3.552	288	3.704	360	3.401			500	3.130
1-Hydroxy-4-acetamidophenazine	242	4.331	282	4.593	368	3.648			475	3.334
1-Methoxy-4-acetamidophenazine	242	4.442	278	4.567	365	3.704			460	3.371
1,4-Diacetamidophenazine	245	4.562	278	4.775	365	3.903			460	3.596
1,4-Dimethylaminophenazine	242	4.619	312	4.562					±600	±3.2
1-Acetamido-4-nitrophenazine			260	4.669	365	4.041			420	3.804
1-Methoxy-4-aminophenazine	240	4.537	298	4.514	358	3.387			527	3.161
1-Amino-6-methoxyphenazine	252	4.411	290	4.543	390	4.047			485	3.286
1-Amino-6-hydroxyphenazine	258	4.408	288	4.508	395	3.992			480	3.373
1-Amino-6-acetoxyphenazine	240	4.419	292	4.585	375	3.764			495	3.305
1-Acetamido-6-methoxyphenazine			262	4.742	385	4.169				
1-Acetamido-6-hydroxyphenazine			264	4.801	386	4.069	390	4.093		
2-Aminophenazine	230	4.430	275	4.706	362	3.816			468	3.884
2-Aminophenazine in N/10 HCl	231	3.819	281	3.961	383.5	3.344			518	3.382
2-Methylaminophenazine			282	4.668	370	3.850			472	3.986
2-Nitrophenazine ?	240	4.532	282	4.408	368	4.063				
1-Methoxy-6(or 7)-nitrophenazine	248	4.524	300	4.427	358	3.659			428	3.304
1-Methoxy-5(or 8)-nitrophenazine			265	4.658	365	3.927			422	3.455

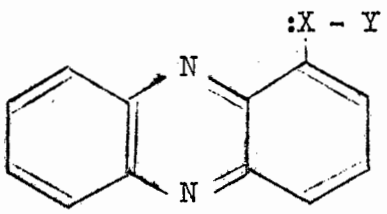
1-Hydroxy-4-nitrophenazine in alcohol did not obey Beer's Law. 1-Acetoxy-4-acetamido- and 1-acetoxy-4-aminophenazine deviated from Beer's Law, at high dilutions made for the readings at the shorter wavelengths. Unfortunately, due to trouble with the spectrophotometer, the absorption spectra of all these compounds could not be determined.

Because of possible interference from fluorescence there was the danger of distortion in this photoelectric method of determining the spectra of these compounds[95].

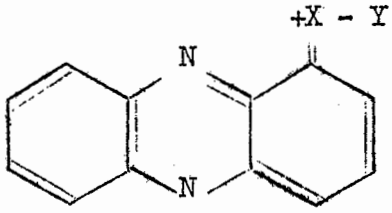
It was hoped to find some empirical correlation between the ultraviolet light absorption and molecular structure. The observations made on the following pages are purely descriptive of the spectra of these phenazines and are not generalisations or predictions for all phenazines. With such a limited number of spectra of these compounds available any sound generalisation would be almost impossible.

The absorption spectra of this group of compounds show a general similarity. The absorption maxima can be classified into four groups A, B, C and D in the regions of 240, 270, 370 and 400 - 500 mμ respectively. Not all these bands are always present although the bands B and C are shown in all the compounds examined except for 1,4-dimethylaminophenazine. Two bands corresponding to these are found in phenazine itself at 250 mμ and 370 mμ[96]. These must presumably represent the absorption bands of the partial chromophore persisting in the series of substituted phenazines, although the presence of the substituent modifies their position to some extent, more so in the case of the shorter wavelength band than in that of the longer, which except for 1,4-dimethylaminophenazine where it has become only an inflexion at 380 mμ, persists in the region of 370 mμ as a pronounced peak.

Besides modifying the position of bands B and C, the presence of substituents may cause the development of other bands. This is particularly so when the substituent group has, directly linked to the phenazine nucleus, an oxygen or a nitrogen atom i.e. an atom which carries a lone pair of electrons, which can become shared with the nucleus in a resonance structure which involves structures such as I and II for a substituent in the 1 position

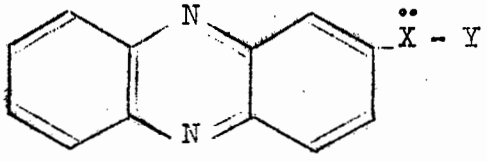


I

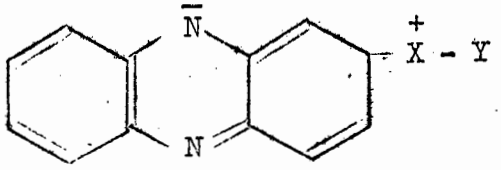


II

and III and IV for a substituent in the 2 position



III



IV

Resonance is held to cause absorption at long wavelengths. One of the theories proposed as a reason why resonance should produce absorption at long wavelengths, is that the large number of intermediate ionic forms contribute mainly to resonance in the excited state, thus resulting in a marked lowering of the energy in the latter state[97], the energy required to raise the molecule from its ground state to the excited state is then relatively small, and so absorption occurs at long wavelengths ($E'' - E' = h\nu = h^c/\lambda$). The introduction of an auxochrome which will stabilise the participating ionic forms, such as indicated by II and IV will therefore be expected to show an absorption band at long wavelengths, due to lowering of the energy of the excited state. In those

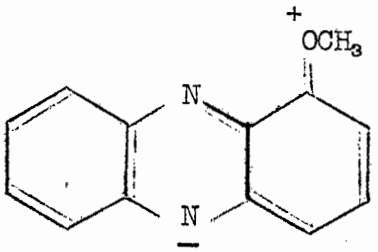
compounds with such auxochromic groups present the long wavelength band D appeared.

The absorption curves of 1-amino- and 2-aminophenazine are good examples of the type of curve these compounds gave. The character of these curves is maintained throughout, although in some cases the selective intensities of the various bands were suppressed relative to each other to such an extent that they no longer appeared as an individual peak but only as an inflexion on the curve. In the case of 1,4-dihydroxy-, 1-acetoxy-4-amino-, 1-amino-, 1-methylamino- and 1-acetamido-6-hydroxyphenazine the peak of band C was split to give two small peaks.

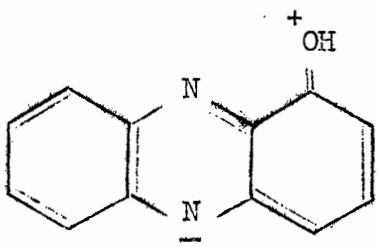
The effect of various substituents on the absorption spectra will now be discussed.

The spectra of 1-hydroxy-, 1-methoxy- and 1-acetoxyphenazine are similar. The long wavelength band moves to shorter wavelengths in this order. The band D was incorporated into band C for 1-acetoxyphenazine.

Due to the greater electron repelling effect of the methyl group as compared to a hydrogen atom it was expected that the oxygen atom of the methoxy group would share its electron pair more readily than the oxygen atom of the hydroxy group. The resonance structure V for 1-methoxyphenazine could thus be expected to be more stable than **VI**, the resonance structure for 1-hydroxyphenazine, and consequently the energy difference between the excited and ground states for 1-methoxyphenazine smaller than for 1-hydroxyphenazine. In the light of this argument it was unexpected to find that band D was at longer wavelengths for 1-hydroxyphenazine than for 1-methoxyphenazine.



V

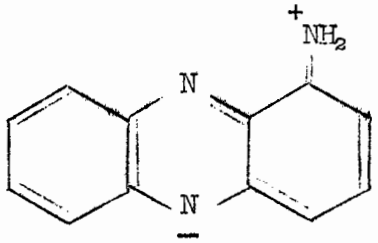


VI

Due to the electron attracting effect of the acetyl group the electron pair of the oxygen atom linked to the phenazine nucleus in 1-acetoxyphenazine cannot be readily shared. Resonance of the type VI for 1-hydroxyphenazine, will not be important, and there is no absorption band at long wavelength and little change in the absorption spectrum as compared to phenazine.

In the case of an amino group, the sharing of such a lone pair of electrons will be particularly pronounced and thus 1- and 2-aminophenazine show a marked development of the long wavelength band D.

The long wavelength band D in the spectrum of 1-aminophenazine is at considerably longer wavelengths than the D band of 1-hydroxyphenazine. Due to the stronger basicity (increase in electropositivity) of the N atom as compared to the oxygen atom, a resonance structure such as II, will have a lower energy for 1-aminophenazine (VII) than for 1-hydroxyphenazine.



VII

VII being more stable than VI, the energy required to raise 1-aminophenazine to its excited state will be less than for 1-hydroxyphenazine and thus absorption will result at longer wavelengths.

There is very little difference between the absorption spectra of 1-amino- and 1-methylaminophenazine. The most prominent difference is the shifting of the long wavelength absorption band to longer wavelengths and an increase in the molecular extinction coefficient of this band for the methylamine compound. This was an expected difference due to the increase in basicity of the N atom of the 1-amino group, and thus lowering of the energy of the resonance state (VII) due to the greater electron repelling effect of a methyl group as compared to a hydrogen atom.

Band D for 2-aminophenazine was at slightly shorter wavelengths than for 1-aminophenazine. 2-Methylaminophenazine had all its absorption bands shifted to slightly longer wavelengths than those of 2-aminophenazine.

Both 1-aminophenazine and 2-aminophenazine have their long wavelength band shifted to longer wavelengths, broadened and the intensity of this band appreciably reduced when dissolved in N/10 hydrochloric acid.

The proton on the 10 nitrogen atom of the azine ring results in the electron pair of the nitrogen in the 1-amino group being more readily shared, or donated and thus a lowering of the energy of the resonance hybrid. Similarly a proton on the 9 nitrogen atom of the azine ring lowers the energy of a similar resonance hybrid in the case of the 2-amino compound. The effect of acid on the spectrum of 2-aminophenazine differs from that on 1-aminophenazine in that the absorption intensity of all the bands is decreased for 2-aminophenazine, whereas for 1-aminophenazine only bands B and D were suppressed, the other two maxima being raised.

The introduction of a methyl group onto the amino group of 1-aminophenazine and the addition of a proton onto the 10 nitrogen atom of the azine ring which all tend to lower the energy of the

resonance state VII causeing a shift to longer wavelengths. The introduction of a group onto the 1-amino group which will decrease the case whereby the electrons may take part in a resonance structure such as VII will raise the energy of the excited state and should thus result in a shifting of the band D to shorter wavelengths. This was found to be so. On introducing the electron attracting acetyl group onto the amino group of 1-aminophenazine there was a shift of the D band by approximately 90 mμ to shorter wavelengths.

The introduction of a second auxochrome into the phenazine nucleus makes the attempt at correlation of structure and absorption spectra more difficult. In compounds of this type the effect of auxochromes is not additive as the electronic structure of the molecule as a whole is modified, due to electronic interaction of the various groups capable of resonance.

Introduction of a nitro group into the 4 position of 1-amino-, 1-acetamido- and 1-methoxyphenazine had hardly any effect on the absorption curves of these compounds. Both the positions and the intensities of the absorption bands of these compounds remained almost unchanged. As it was found that the introduction of a nitro group into the 4 position of these compounds had so little effect on their absorption spectra, a similar result was expected on comparison of the spectrum of 1-acetoxy-4-nitrophenazine with that of 1-acetoxyphenazine. This was found to be so with the short wavelength bands at 250 mμ and at 370 mμ, where the peaks shifted by no more than about 3 mμ and their heights also remained practically unchanged. However, 1-acetoxy-4-nitrophenazine had a small absorption band at 510 mμ, whereas 1-acetoxyphenazine did not show a band anywhere near this wavelength. This difference in the influence of the introduction of a nitro group in the 4 position, on the absorption spectrum of 1-acetoxyphenazine, as compared to these other compounds may be real. On the other hand the appearance of this band at long wavelength could

be due to hydrolysis of the acetoxy group and thus the presence of a hydroxy group in the molecule. Supporting this suggestion is the fact that on the introduction of an auxochrome, such as the hydroxy group, into a molecule, absorption at long wavelengths could be expected and also that the yellow alcoholic solution of 1-acetoxy-4-nitrophenazine was found to turn reddish on standing in alcohol for some time. 1-Hydroxy-4-nitrophenazine, the hydrolysis product of this compound has a similar reddish colour in alcoholic solution to that observed here.

The introduction of a nitro group into the 5 (or 8) position does not alter the spectrum of 1-methoxyphenazine much. The bands B and C of 1-methoxy-5(or 8)-nitrophenazine are shifted to longer wavelengths by only 5 mμ as compared to those of 1-methoxyphenazine. At longer wavelengths there is a more pronounced shift of the band. Band D is shifted by 20 mμ to longer wavelengths. As compared to 1-methoxyphenazine, 1-methoxy-6(or 7)-nitrophenazine has its absorption bands A and B displaced to longer wavelengths, band C is hardly changed in position and band D is moved to longer wavelengths. Evidently the introduction of a nitro group in the 4 position does not affect the energy difference between the ground and the excited state as much as when it is introduced into the 5 (or 8) or the 6 (or 7) position.

In the absorption spectrum of 1-methoxyphenazine the long wavelength band D is at 402 mμ and not well defined at all. This band has disappeared completely in the spectrum of 1-acetoxyphenazine. However on the introduction of an amino group in the 4 position of these two compounds, a D band appears at very much longer wavelengths in the case of 1-methoxyphenazine and in the case of 1-acetoxyphenazine appears at 498 mμ as a well defined band. The short wavelength peaks are also moved to longer wavelengths. Band B shifts by about 40 mμ and the long wavelength band D by about 120 mμ to longer wavelengths. Band C is not shifted much but the intensity of absorption of this band is appreciably decreased.

In accordance with the general rule, similar bathochromic shifts were observed on the introduction of other auxochromes such as the methoxy and acetamido group. The amino group had a greater bathochromic effect than either the acetamido or the methoxy group. The last mentioned two groups had about equal effect.

The introduction of a methoxy group into the 4 position of 1-aminophenazine caused a shift of the D band by 27 mμ to longer wavelengths whereas the introduction of the amino group into the 4 position of 1-methoxyphenazine caused a shift of the D band to longer wavelengths by 125 mμ.

The introduction of the auxochromic hydroxy group into the 4 position of 1-hydroxyphenazine causes a marked bathochromic shift of the long wavelength band D and has distinctive hypochromic effects on bands C and D, as well as splitting band C into two small peaks.

The positions into which the auxochromes are introduced also has an effect on the absorption spectrum. A hypsochromic shift of the long wavelength absorption band results when both a hydroxy and a methoxy group are moved from the 4 position to the 6 position in 1-acetamidophenazine. This shift was much less pronounced for a corresponding move of a methoxy and an acetoxy group in 1-aminophenazine. In the 1,4-series the substituents are in conjugation with different nitrogen atoms of the azine ring, and do not compete against each other. In the 1,6-substituted phenazines the substituents are competing for the same nitrogen atom and there must then be an inhibiting effect on the resonance of this molecule and thus a shifting of the long wavelength band to short wavelengths.

Earlier it had been stated that acetylation of the 1-amino group caused a shift of band D to shorter wavelengths. Consideration is now given to the effect of acetylation of the 1-amino group when there are other substituents present. The acetylation of an amino group

in a 1 position of the phenazine nucleus in all the cases observed here, irrespective of whether the other substituent was in the 4 or 6 position, had the effect of shifting the long wavelength maximum D to shorter wavelengths and of raising the peak of this band. This effect was most noticeable in cases where the other substituent on the phenazine nucleus was in the 6 position. In these cases band D showed this effect to such an extent that it appeared only as an inflexion on the absorption curve. In all cases, except for 1-amino -6-methoxyphenazine, the acetylated product had the short wavelength peaks moved to shorter wavelengths as well. In the 1,6-substituted compounds the intensity of absorption in the shorter wavelength bands is increased, but in the 1,4-substituted compounds hardly changed at all.

As with 1-hydroxyphenazine, acetylation of the hydroxy group in a 4 substituted 1-hydroxyphenazine, had the effect of shifting band D to shorter wavelengths and increasing the intensity of absorption. In the absorption spectrum of 1,4-diacetoxyphenazine as compared to the spectrum of the dihydroxy compound and 1-acetoxyphenazine as compared to the hydroxy derivative, the long wavelength peak, quite distinct for the hydroxy compounds, was barely discernible as an inflexion on band C in the spectra of the acetylated products. However, it was found that the long wavelength band of 1-amino-6 -hydroxyphenazine shifted to longer wavelengths on acetylation of the hydroxy group and that the C band, which had hardly moved in the case of the acetylation of a hydroxy group in the 1,4 compounds had moved by 20 mμ to shorter wavelengths.

The powerful auxochromic effect of the amino group is illustrated by the following example. In 1-amino-6-hydroxyphenazine the amino and the hydroxy group compete for the same nitrogen atom of the azine ring for resonance. On acetylation of the hydroxy group and effectively removing the competition from the hydroxy group, there is very little change in the spectrum, in fact there is a shift of the D band to

slightly longer wavelengths. However on acetylation of the amino group, thereby decreasing the possibility of the lone pair of electrons on the amine nitrogen to take part in resonance there is an extremely marked shift of the D band. It now appears only as an inflexion in the absorption spectra.

For the corresponding 1,4 series where the amino and the hydroxy groups do not compete for the same azine nitrogen atom for resonance there is very little difference between the absorption spectra of 1-acetamido-4-hydroxyphenazine and 1-acetoxy-4-aminophenazine. There is only a slight shift of band D to longer wavelengths in the spectrum of 1-acetoxy-4-aminophenazine as compared to 1-acetamido-4-hydroxy-phenazine.

The absorption spectra of 1-hydroxy- and 1-methoxyphenazine being so similar it was not surprising to observe that the exchange of a hydroxy group for a methoxy group in these series of compounds had very little effect on either the wavelength of the absorption maxima or on the intensity of absorption.

An interesting observation was that the spectrum of 1-methoxy-phenazine was almost identical with that of 1-acetamidophenazine. The much greater basicity of the nitrogen atom of the amino group, than the basicity of the oxygen atom of the methoxy group, is decreased to the same level as that of the oxygen atom by the introduction of the electron attracting acetyl group onto the amino group. These two groups could be exchanged in these molecules without affecting the spectrum to any extent at all.

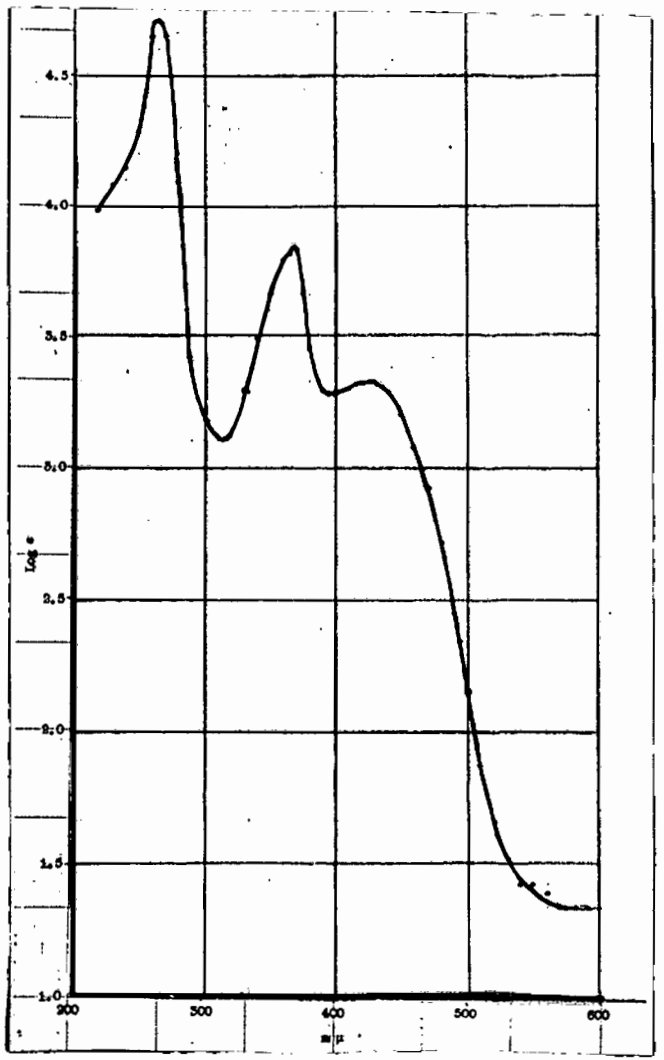
As interaction of the electromagnetic radiation in this, the ultraviolet and visible region is determined by the electronic structure of the molecule[98] (due to the similarity of the energy of the photons in this region and the energy required for the electronic transitions) and as the chemical reactivity of a molecule is dependent on its electronic structure it could be expected that

1-methoxy- and 1-acetamidophenazine would have similar chemical properties. They would thus be expected to have similar orientative properties. This was proved chemically by the cross conversion of members of the series obtained from the nitrated products of these compounds; the nitro group on nitration of these two compounds had in both cases entered the 4 position.

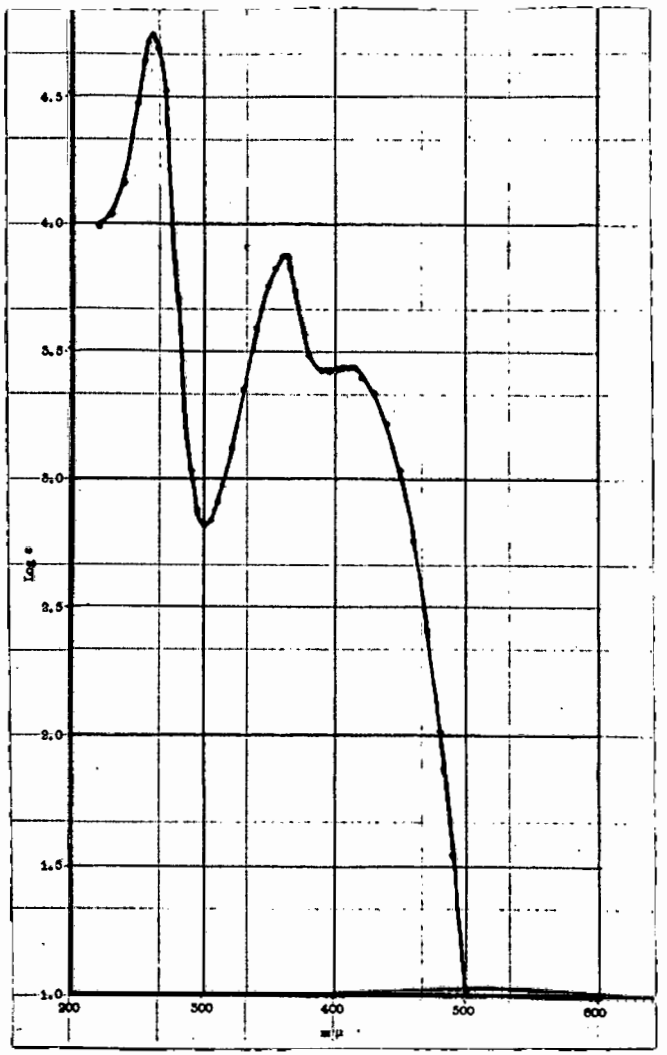
If chemical means had failed to show the similarity in the orientation of these two series of compounds, the similarity in the influence of the introduction of either a methoxy or an acetamido group into a 1 position of the phenazine nucleus on the absorption spectra could have been used with reasonable assurance for the orientation of these compounds. As the absorption spectra of 1-methoxy- and 1-acetamidophenazine are the same, the introduction of the same group into similar positions of these two compounds should again give identical spectra. Thus, as the mono nitro derivatives of these two compounds were found to have identical spectra and as it was proved chemically that the nitro group had entered into the 4 position of 1-methoxyphenazine, the orientation of the acetamido-nitrophenazine could also be taken as 1,4.

A better example was that the absorption spectrum of 1-methoxy -4-acetamidophenazine was almost identical with that of 1,4-di-acetamidophenazine. Thus the evidence of chemical conversions that these were both 1,4 substituted phenazines is supported by these absorption spectra.

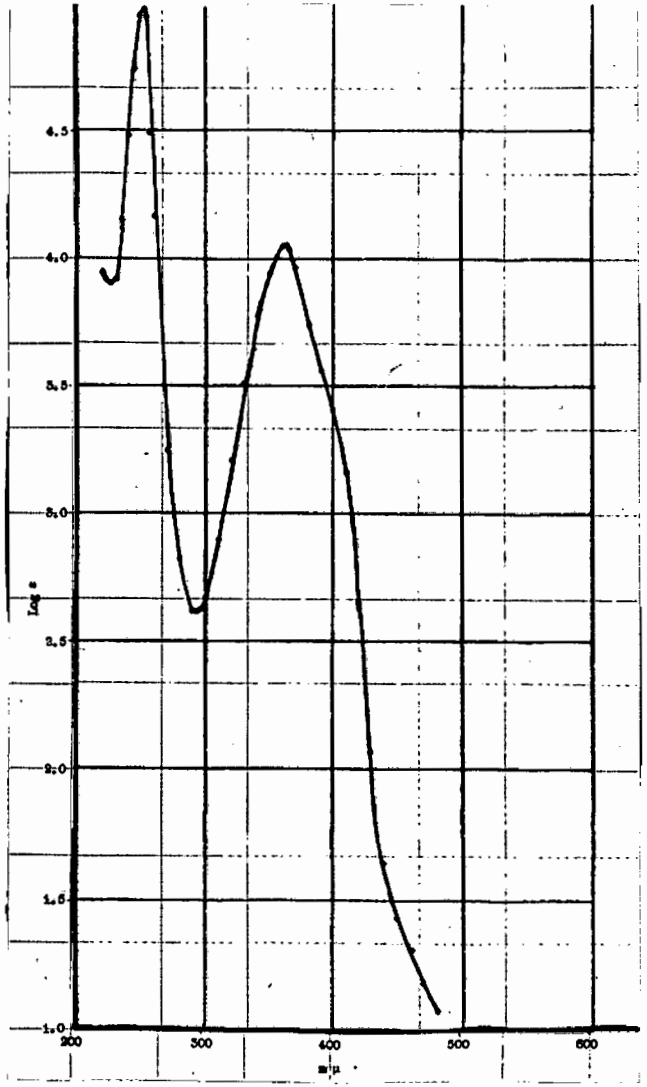
In the light of the relationship between absorption spectra in this region and electronic structure and thus chemical reactivity, it was strange that 1-hydroxyphenazine with a spectrum very similar to that of 1-methoxyphenazine could not be nitrated under similar conditions to those used in the nitration of 1-methoxyphenazine.



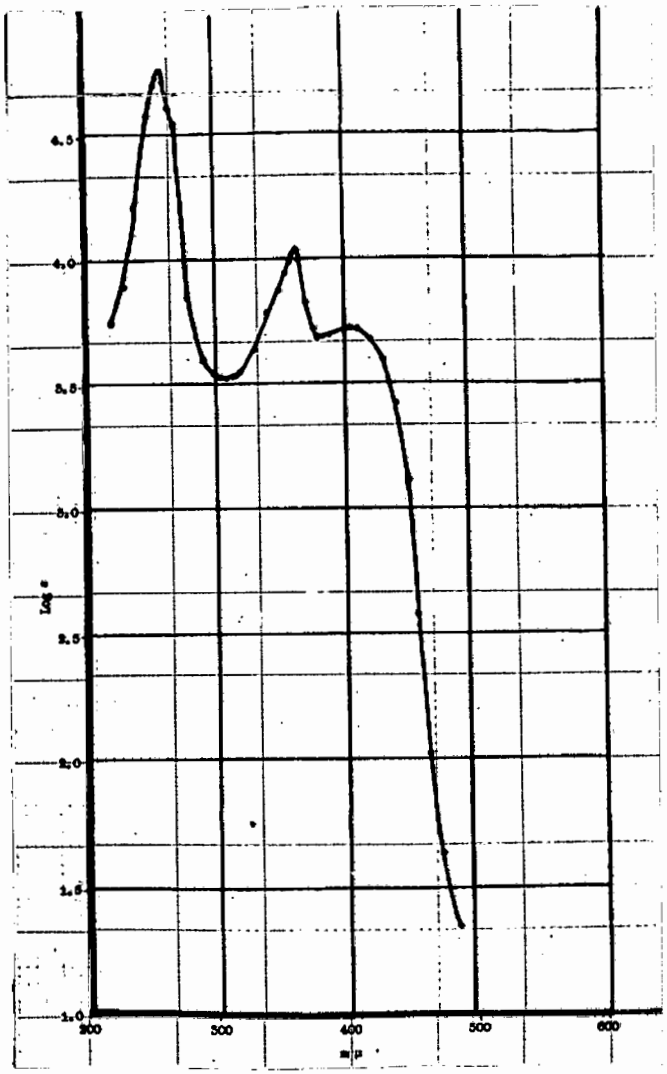
1-Hydroxyphenazine



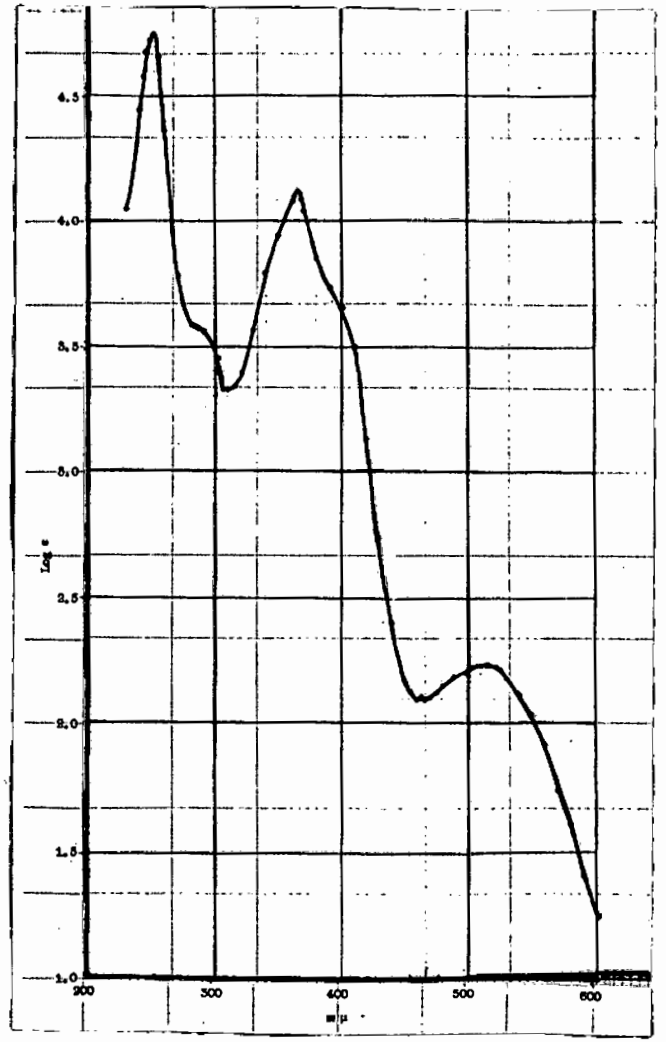
1-Methoxyphenazine



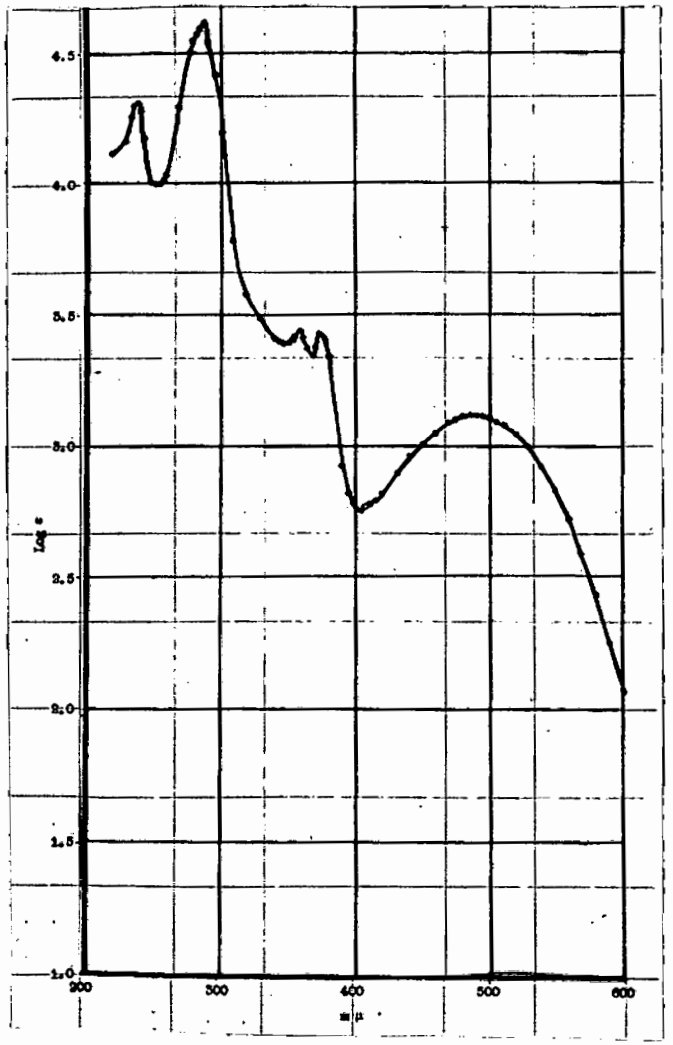
1-Acetoxyphenazine



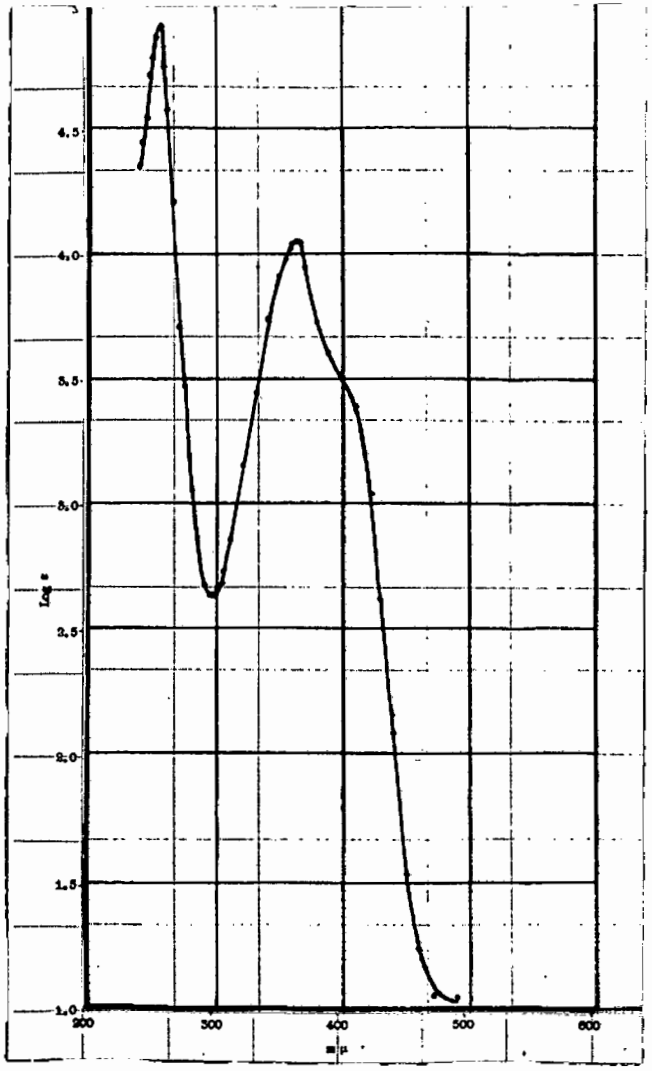
1-Methoxy-4-nitrophenazine



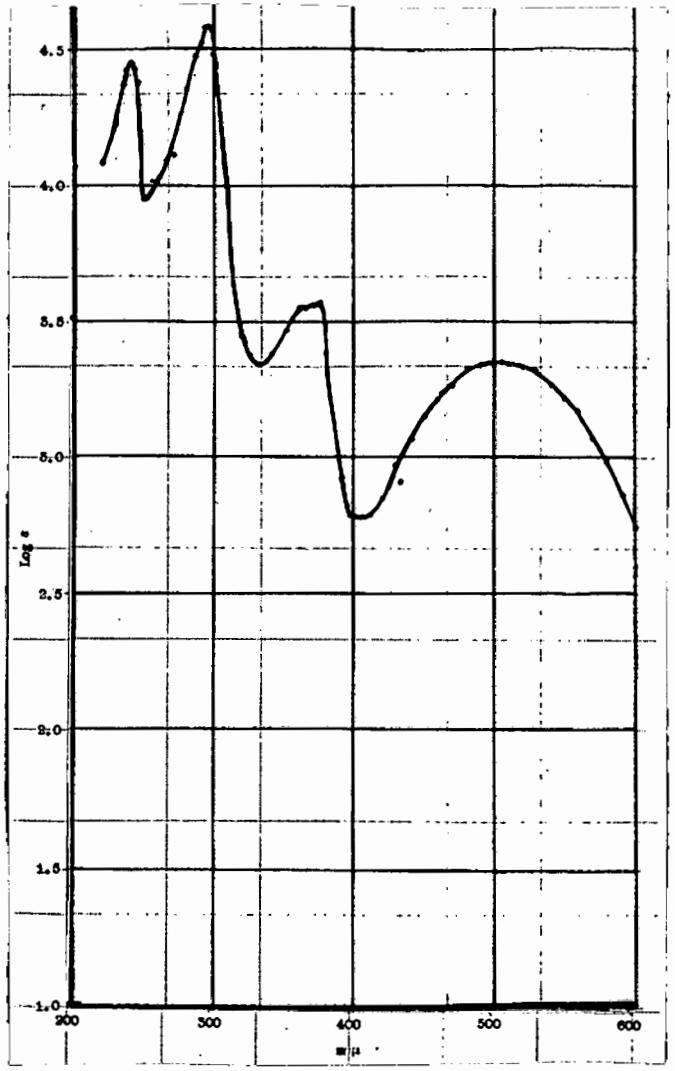
1-Acetoxy-4-nitrophenazine



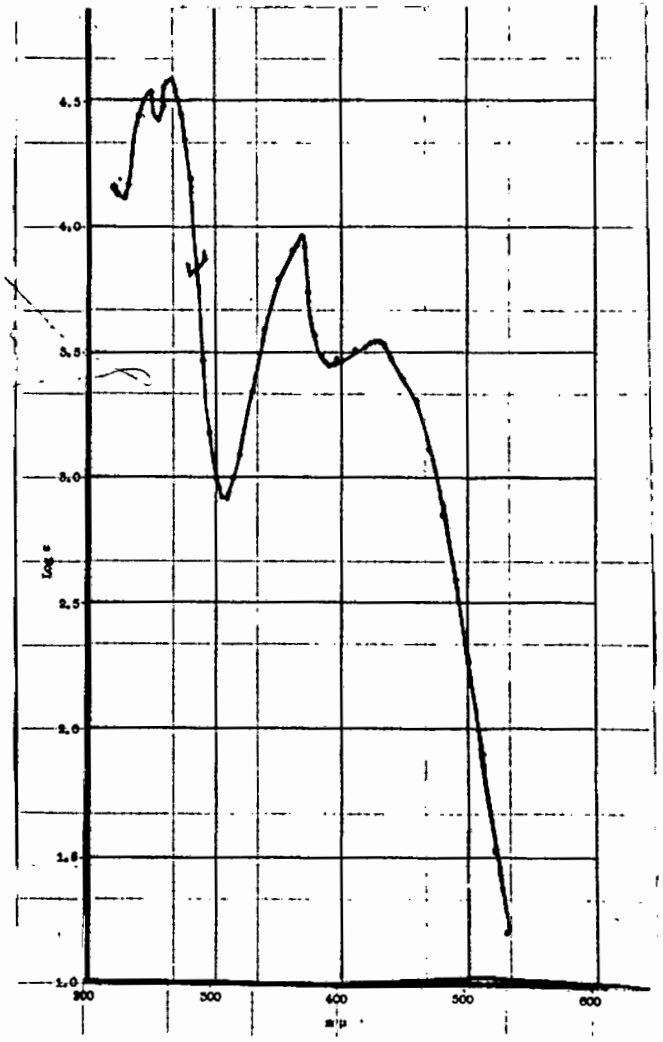
1,4-Dihydroxyphenazine



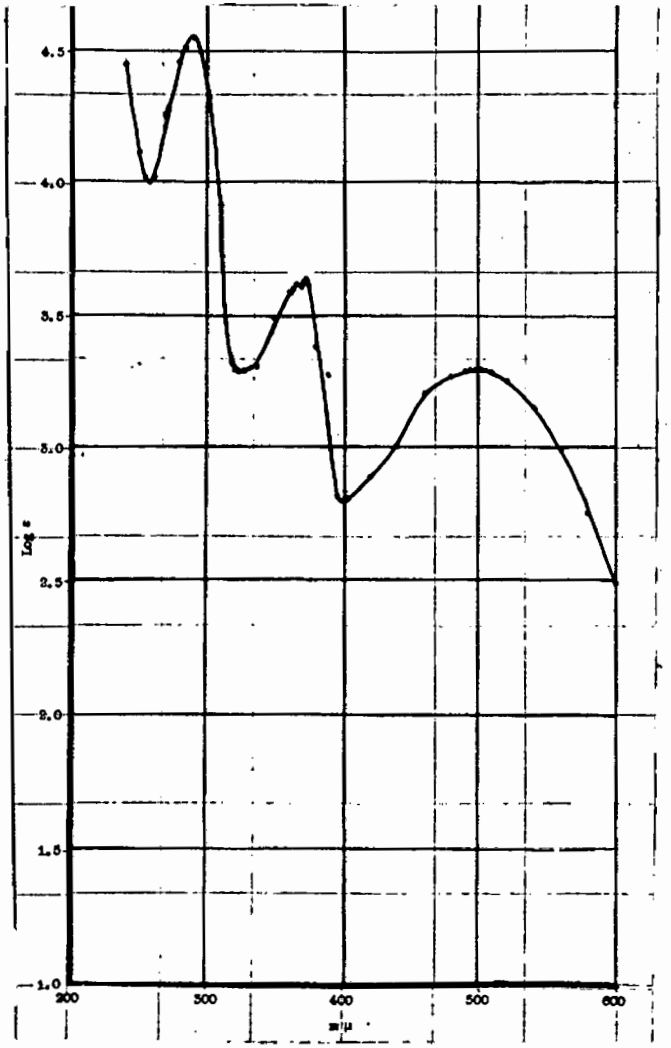
1,4-Diacetoxyphenazine



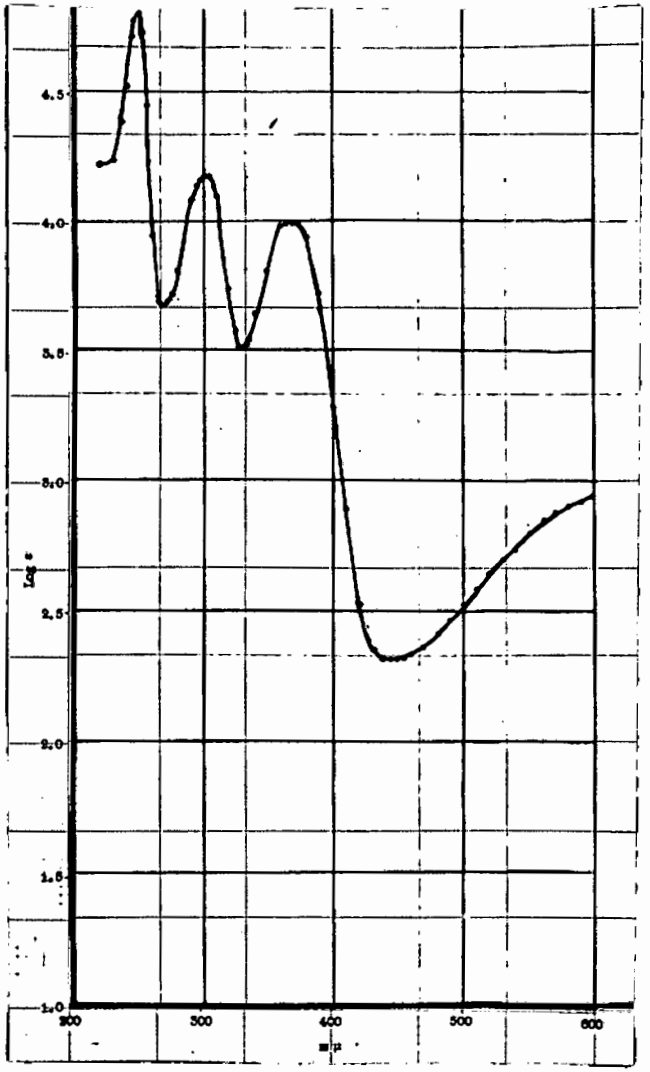
1-Acetoxy-4-aminophenazine



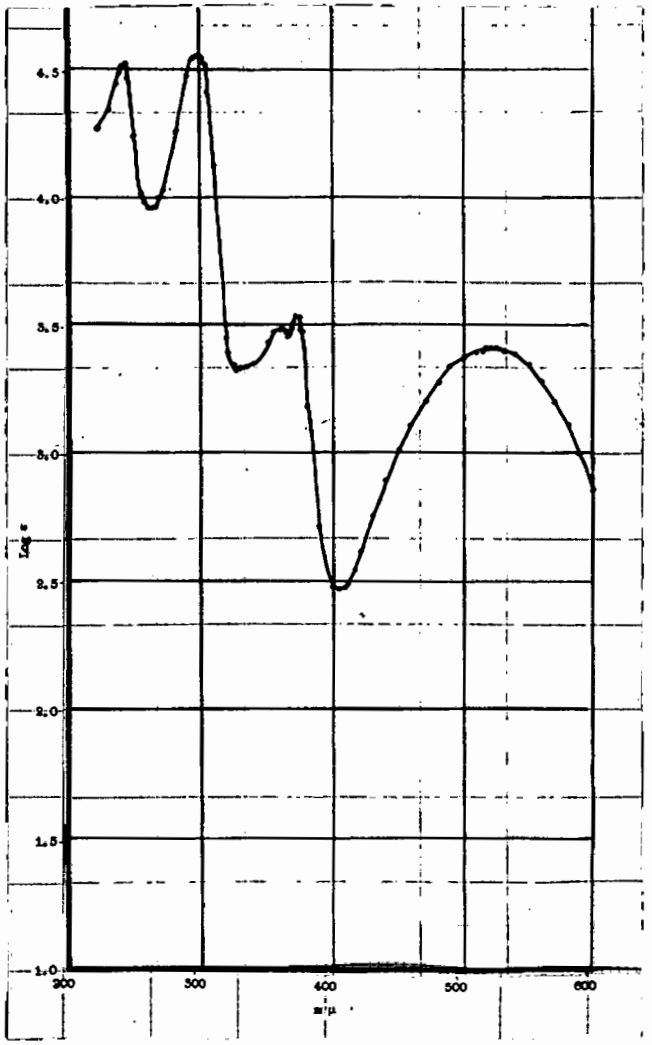
1-Acetoxy-4-acetamidophenazine



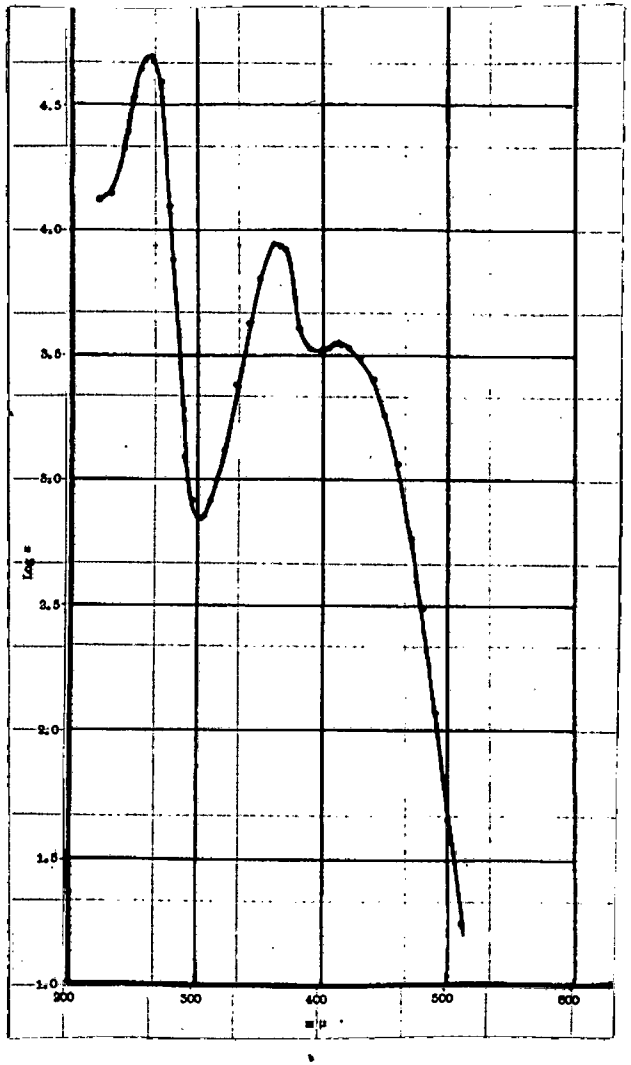
1-Aminophenazine



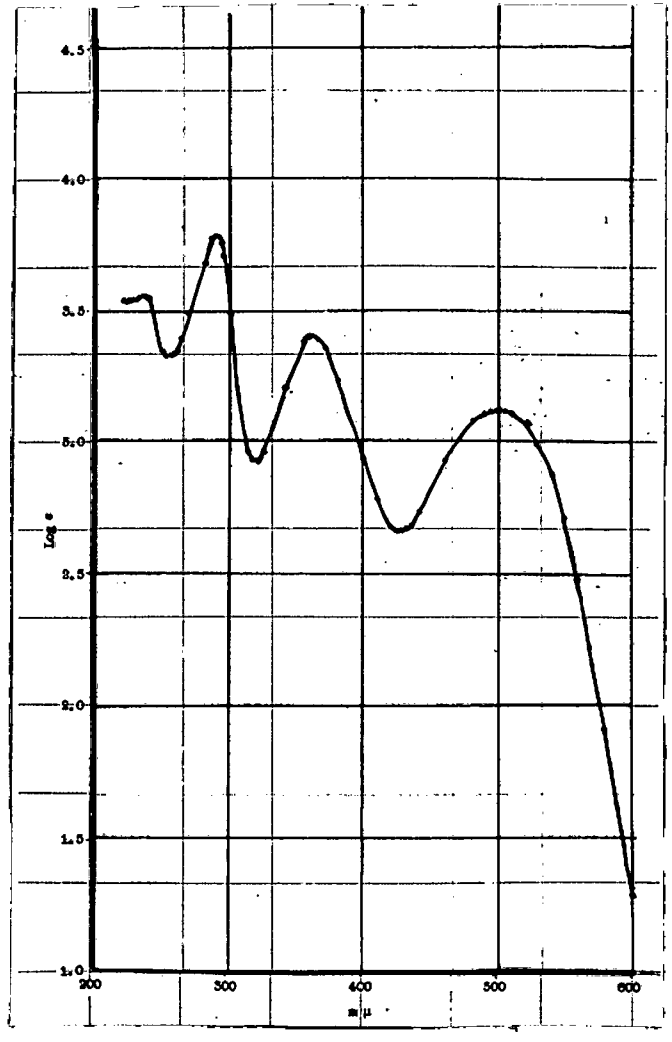
1-Aminophenazine in $^{N}/_{10}$ HCl



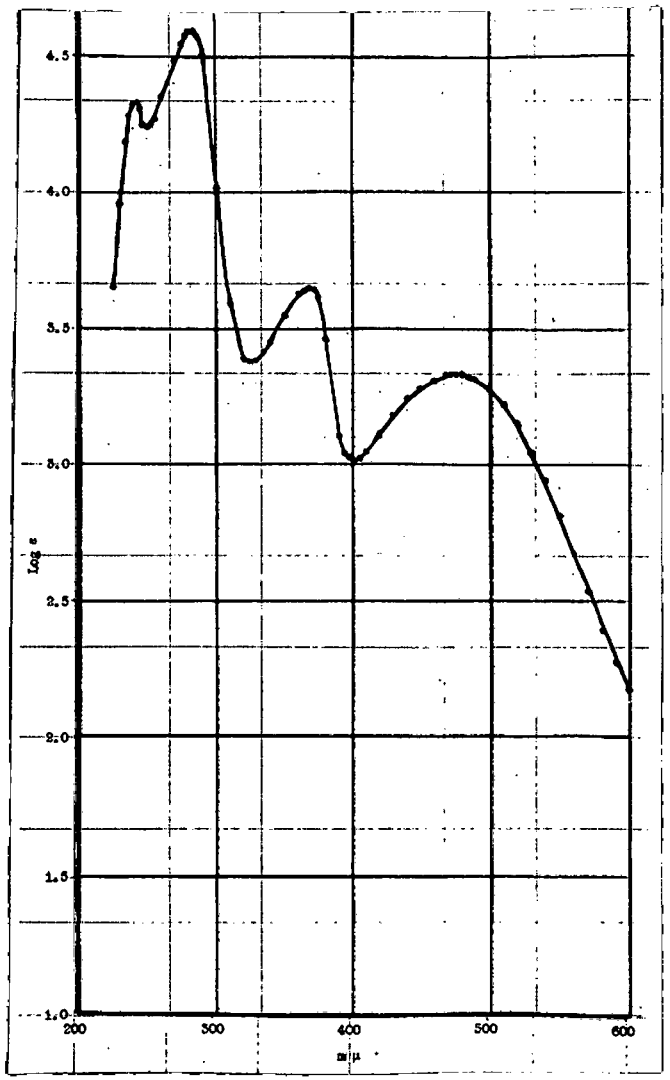
1-Methylaminophenazine



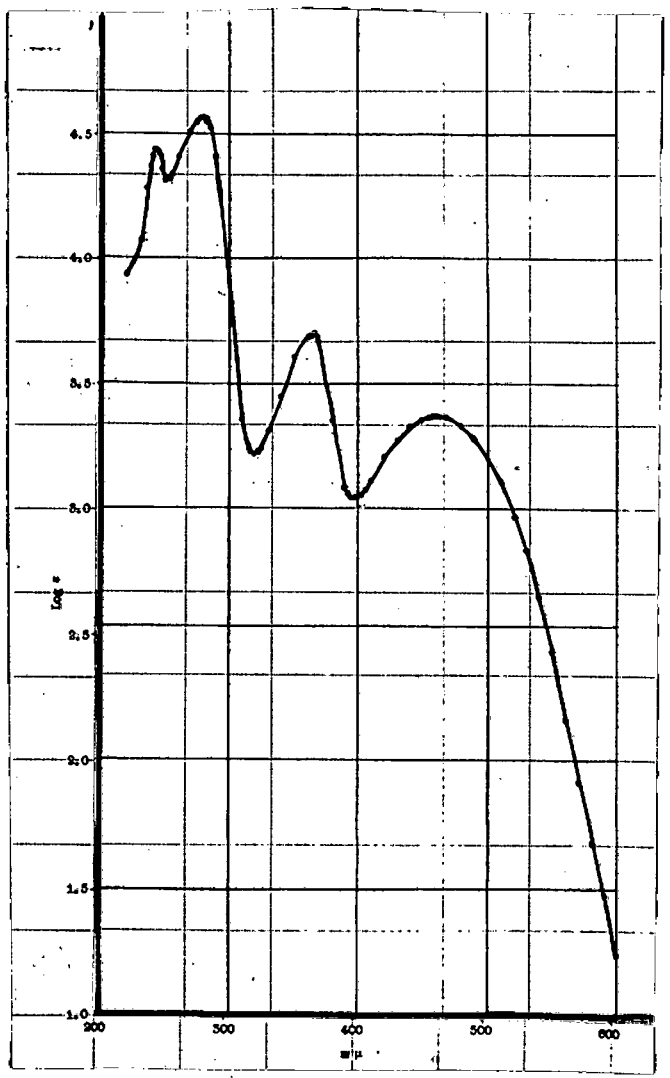
1-Acetamidophenazine



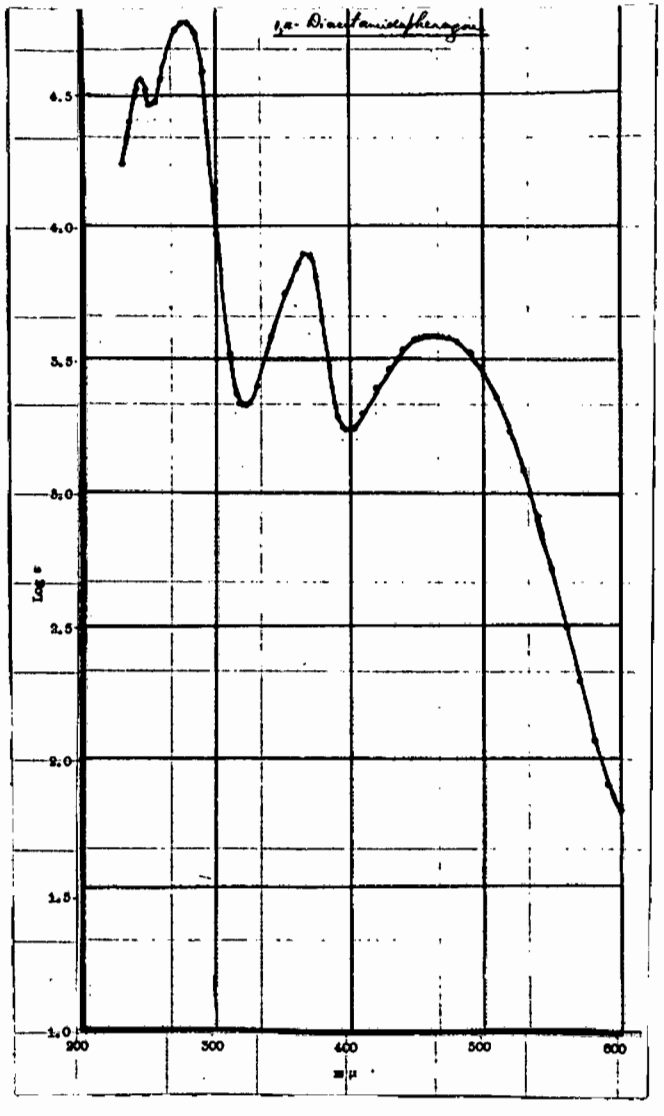
1-Amino-4-nitrophenazine



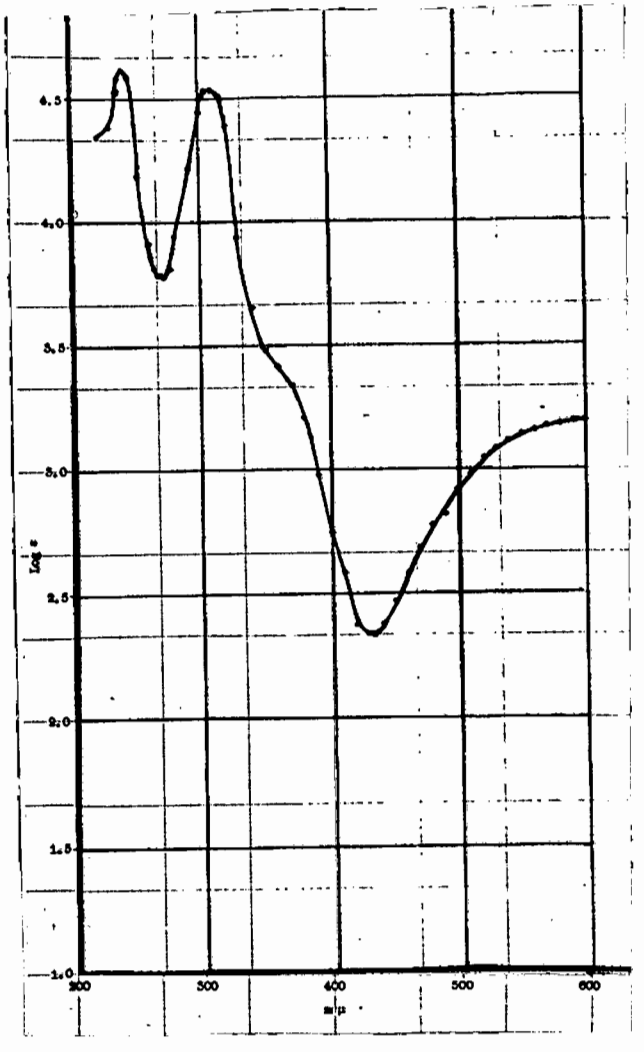
1-Hydroxy-4-acetamidophenazine



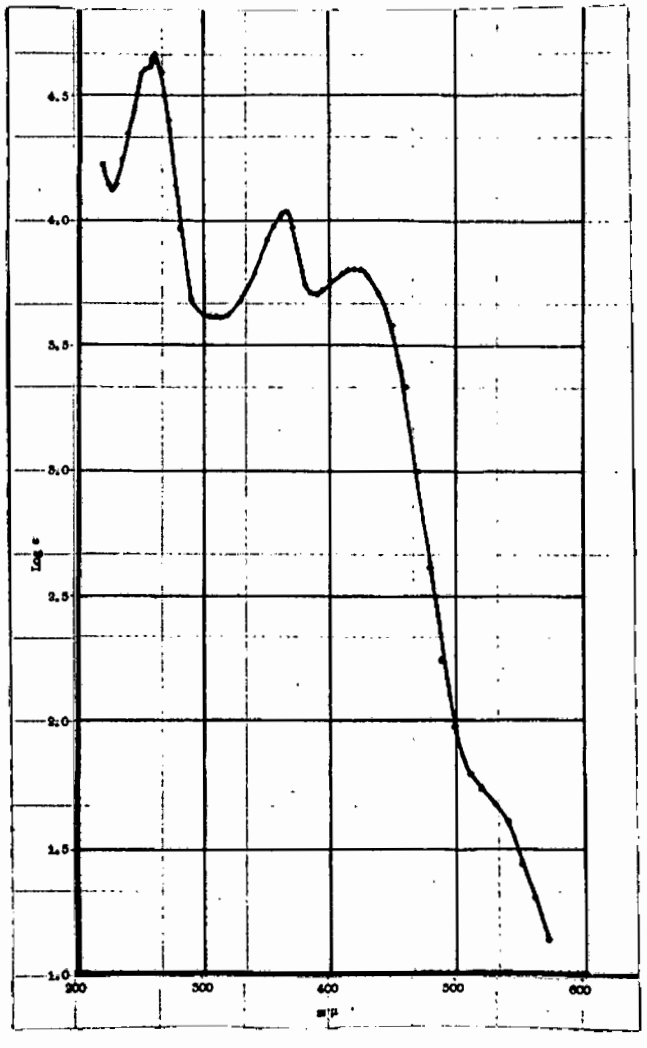
1-Methoxy-4-acetamidophenazine



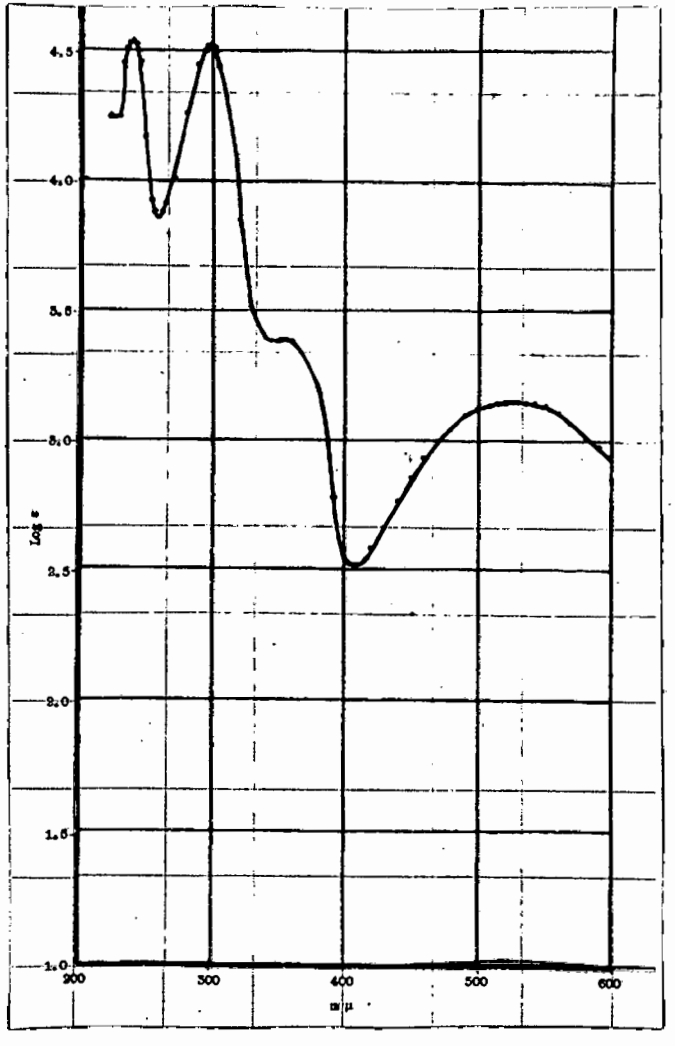
1,4-Diacetamidophenazine



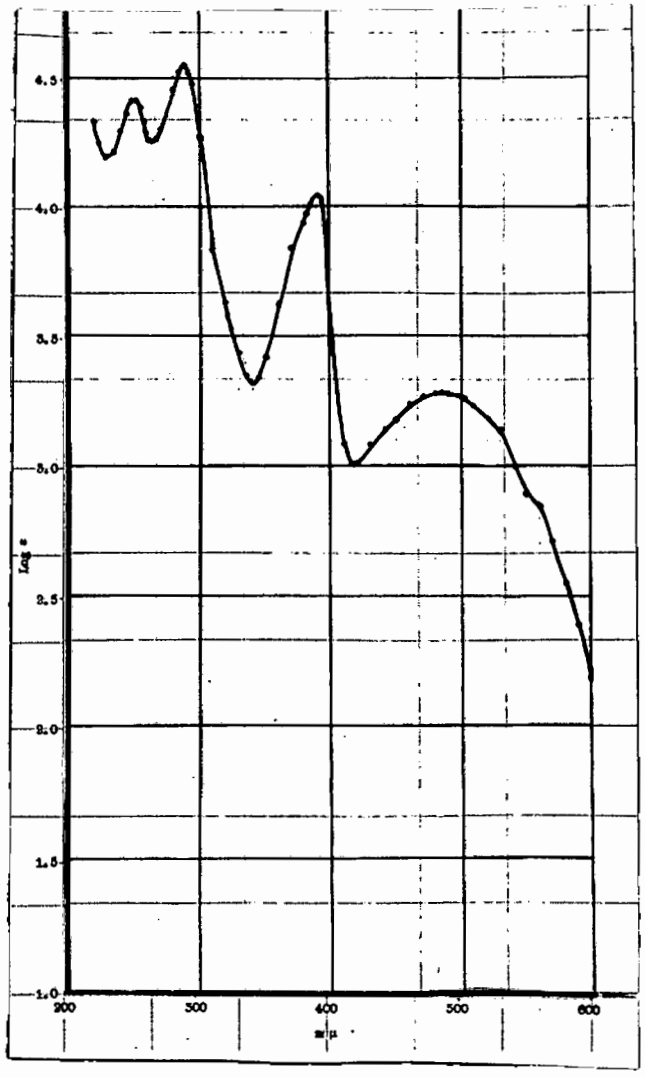
1,4-Dimethylaminophenazine



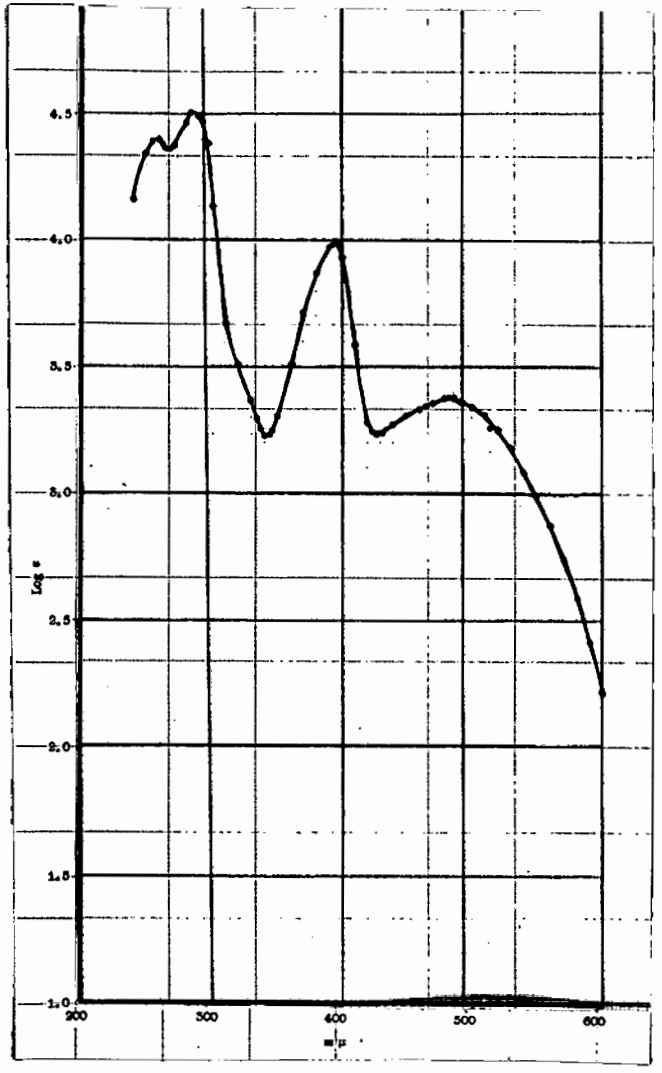
1-Acetamido-4-nitrophenazine



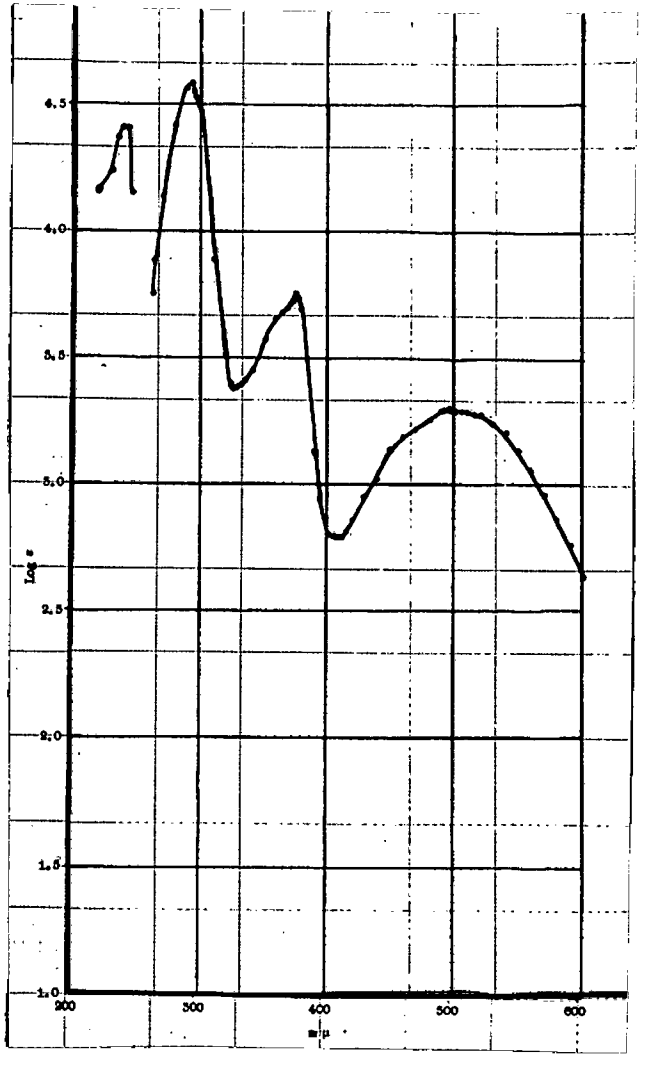
1-Methoxy-4-aminophenazine



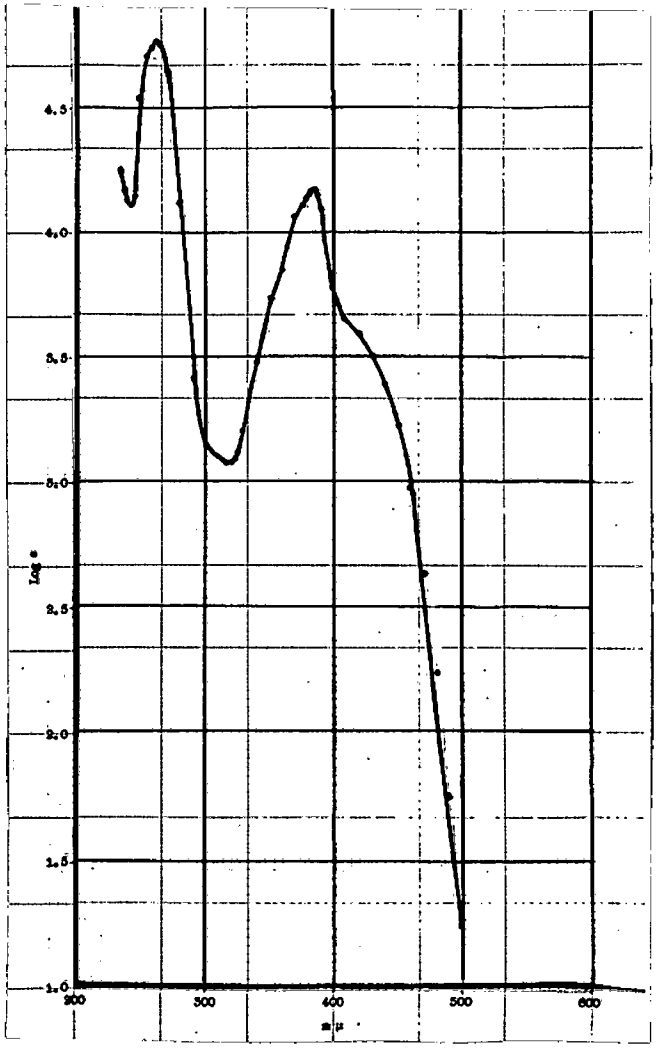
1-Amino-6-methoxyphenazine



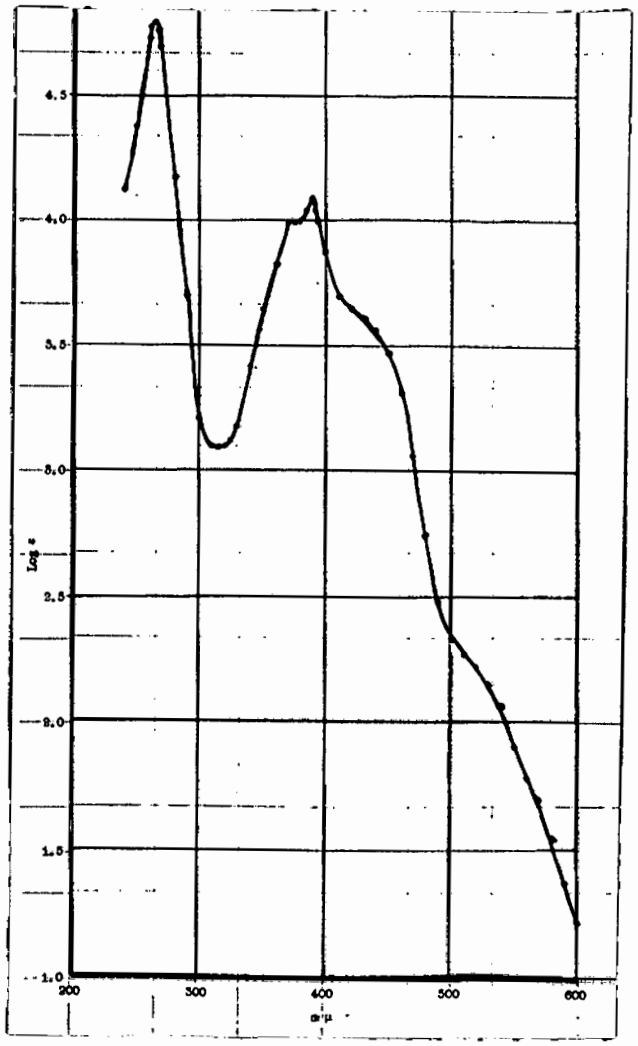
1-Amino-6-hydroxyphenazine



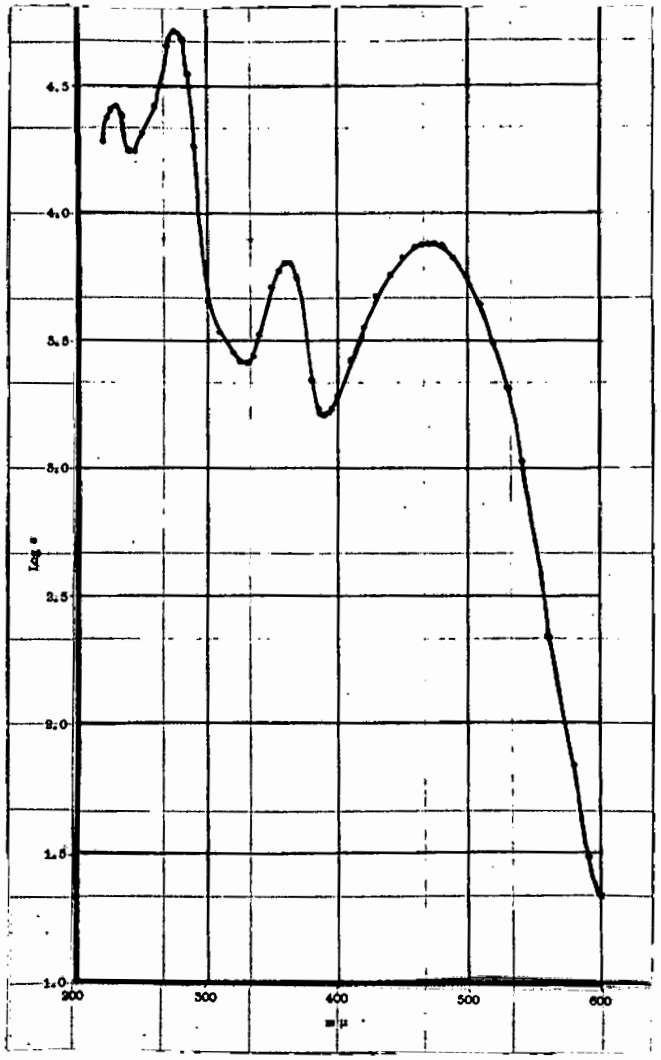
1-Amino-6-acetoxyphenazine



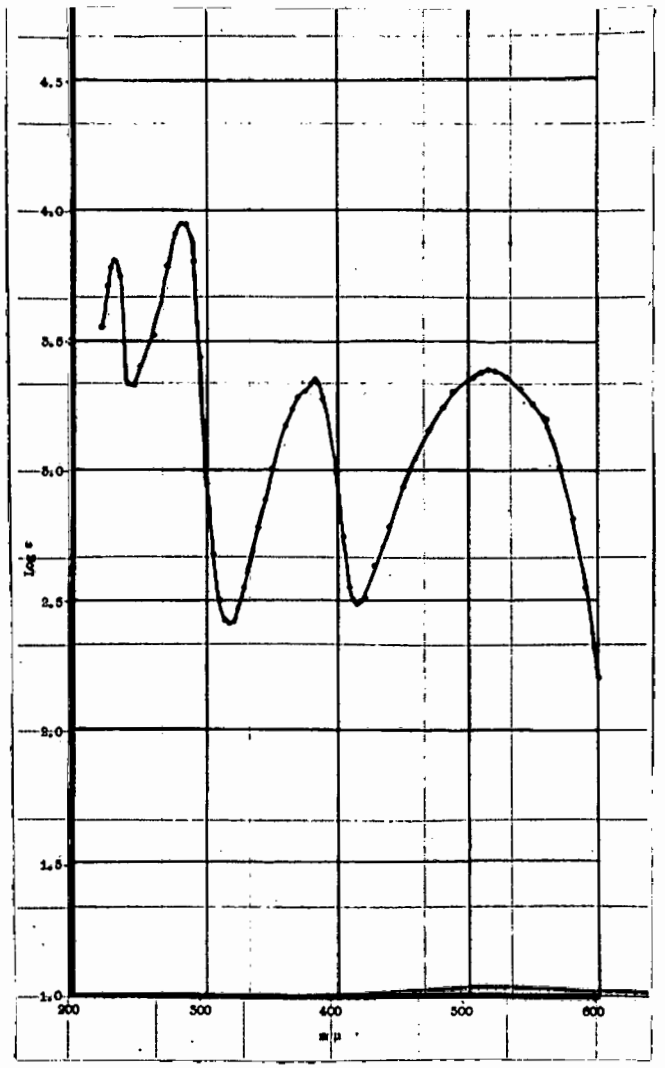
1-Acetamido-6-methoxyphenazine



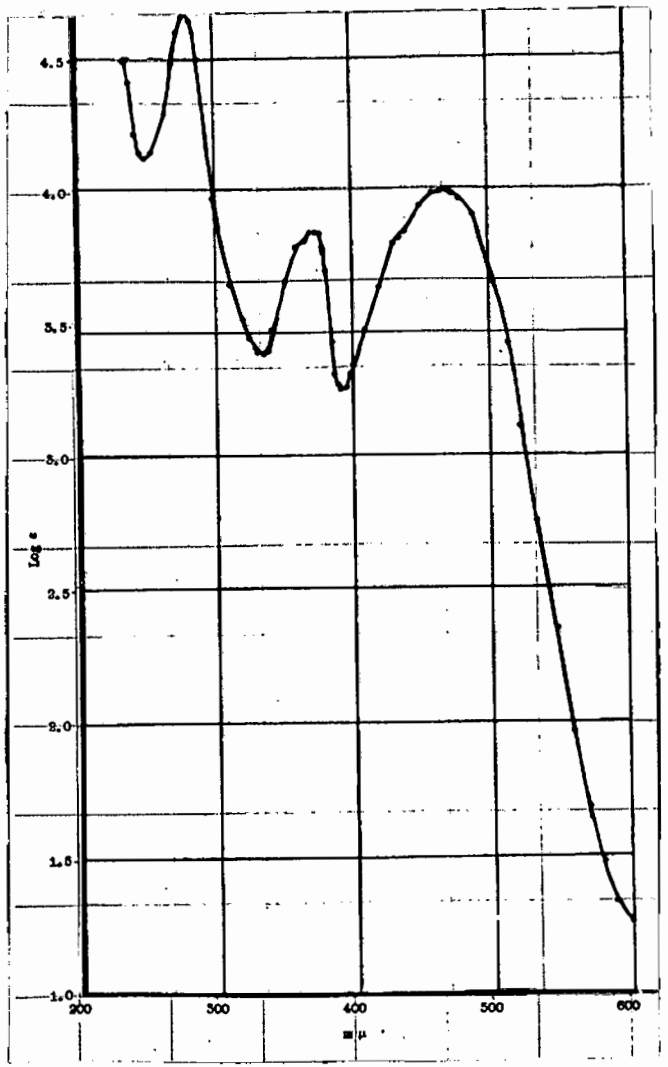
1-Acetamido-6-hydroxyphenazine



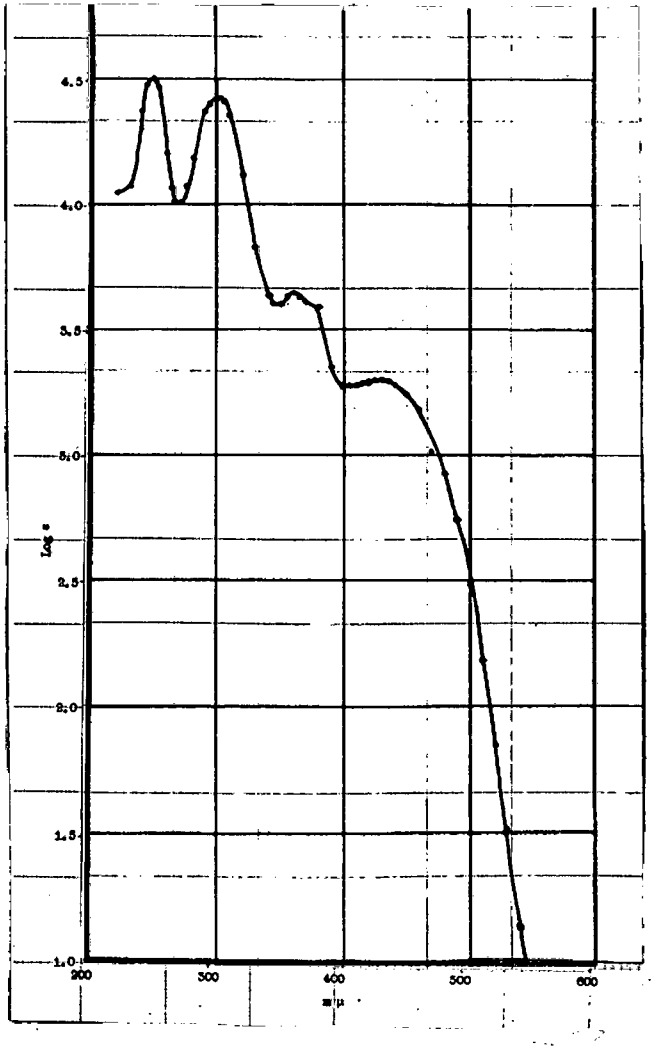
2-Aminophenazine



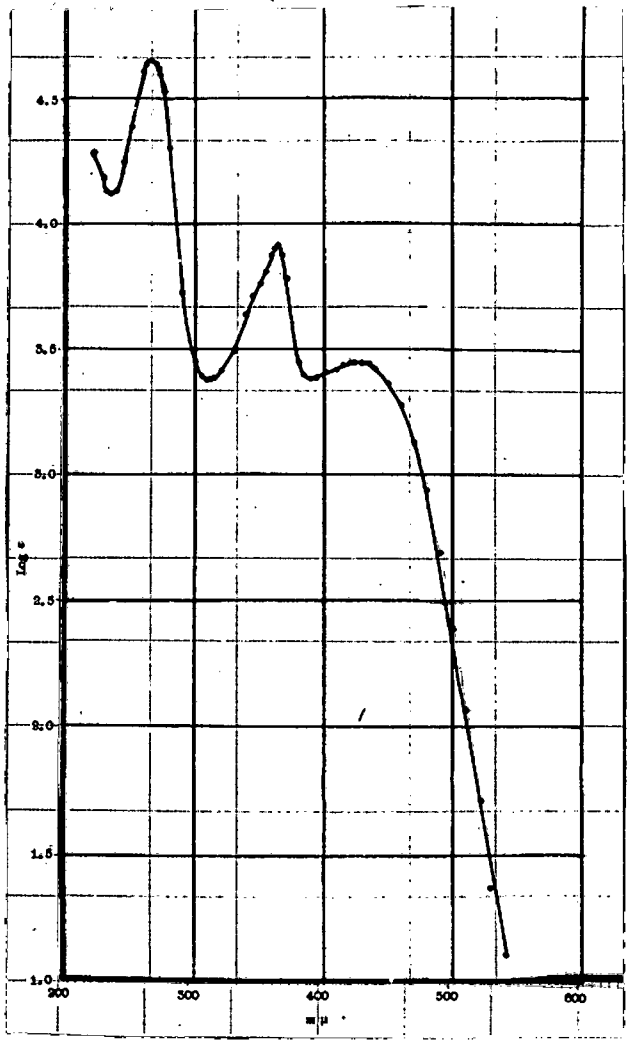
2-Aminophenazine in $^{N}/_{10}$ HCl



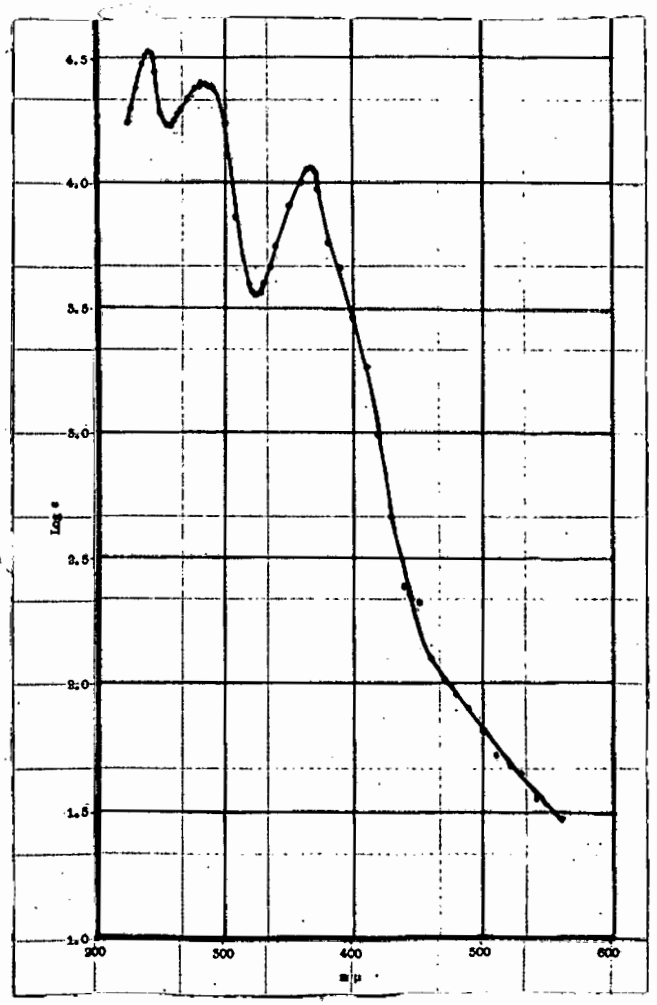
2-Methylaminophenazine



1-Methoxy-6(or 7)-nitrophenazine



1-Methoxy-5(or 8)-nitrophenazine



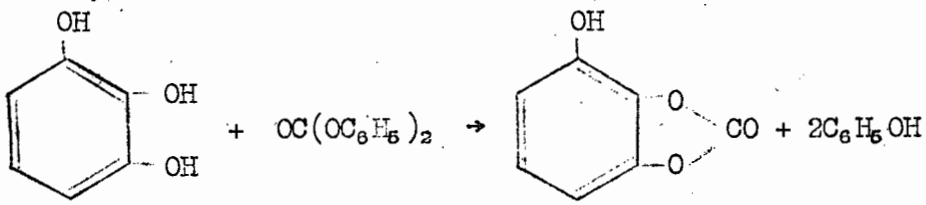
2-Nitrophenazine

E X P E R I M E N T A L.

SECTION IA.

Preparation of pyrogallol carbonate.

A. Einhorn, J. Cobliner and H. Pfeiffer. Ber. 106 (1904)



Pyrogallol carbonate of melting point 130° - 133° was obtained in a 75% yield.

Attempted preparation of pyrogallol carbonate methylether.

6.5 Gms. of pyrogallol carbonate, 5.4 gms. of anhydrous potassium carbonate and 5.5 ml. of methyl iodide were refluxed in 20 ml. of dry acetone for 3 hours, allowed to stand overnight and then refluxed for a further 2 hours. The acetone was distilled off and the residual black mass extracted with ether. On evaporation of the ether a dark brown syrup, which resisted all attempts to make it solidify, was obtained.

Preparation of N-nitrosomethylurea.

F. Arndt. Org. Syn. 14, 48.

$$CH_3NH_2.HCl + KCNO \rightarrow CH_3NH.CONH_2 + KCl$$
$$CH_3NH.CONH_2 + HNO_2 \rightarrow CH_3N(NO)CONH_2 + H_2O.$$

A 78% yield of N-nitrosomethylurea was obtained.

Preparation of diazomethane.

F. Arndt. Org. Syn. 15, 3.

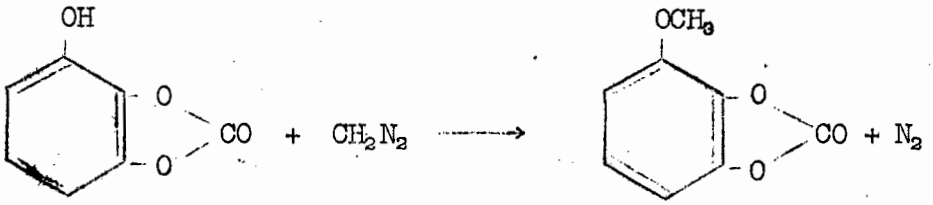
(i) $CH_3N(NO)CONH_2 + KOH \rightarrow CH_2N_2 + KCNO + 2H_2O$

(ii) $C_6H_5COOH + CH_2N_2 \rightarrow C_6H_5COOCH_3 + N_2.$

Diazomethane was prepared and the yield determined as being 75%.

Preparation of pyrogallol-methylether carbonate.

H. Hillemann. Ber. 71, 41, (1938).



A 91% yield of pyrogallol-methylether carbonate, of melting point 109° - 112°, was obtained.

Attempted preparation of pyrogallol-1-monomethylether.

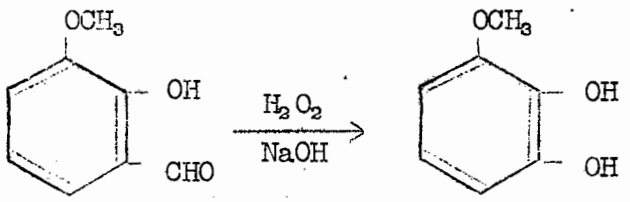
Compare H. Hillemann. Ber. 71, 41 (1938).

40 Gms. of pyrogallol methylether carbonate were boiled in 500 ml. of water for 30 minutes to effect the hydrolysis to pyrogallol-1-monomethylether.

On saturating the solution with ordinary calcium chloride, the reaction solution turned black in a short while and no product could be isolated.

Preparation of pyrogallol-1-monomethylether.

A.R. Surrey. Org. Syn. 26, 90.

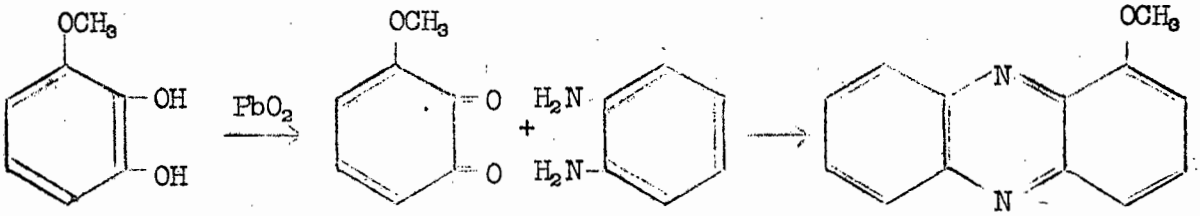


The method described by Surrey was followed, except that the ether extractions and the distillation of the pyrogallol-1-monomethylether were carried out in a nitrogen atmosphere. The yield

varied between 66% and 80%.

Preparation of 1-methoxyphenazine.

A.R. Surrey. Org. Syn. 26, 86.

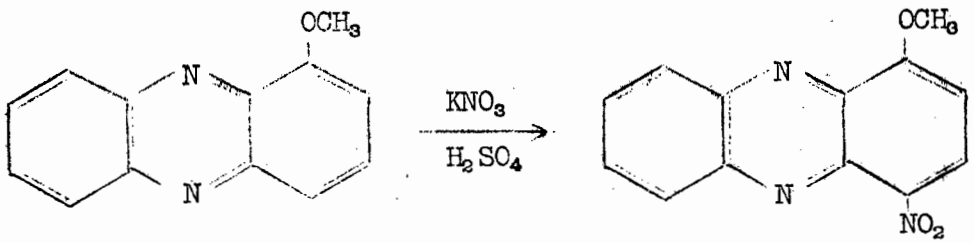


Approximately a 60% yield of crude 1-methoxyphenazine of melting point 165° - 168° was obtained. This product could be used without purification for subsequent reactions. Recrystallised, the yield dropped to 45% of the theoretical yield and the melting point rose to 167° - 169°.

1-Methoxyphenazine was obtained as fine yellow needles, with a yellow fluorescence, on recrystallisation. Dissolved in concentrated hydrochloric acid a red solution is obtained, not changing in colour on dilution.

Preparation of 1-methoxy-4-nitrophenazine.

(i)



To a solution of 7 gms. of 1-methoxyphenazine in 105 ml. of concentrated sulphuric acid, cooled to -8°, 8.9 gms. of potassium nitrate was added with vigorous mechanical stirring. After stirring for about 3 hours, the reaction mixture was allowed to stand for a further 11 hours in the freezing mixture, the temperature rising to 10° during this period, then poured into 1 litre of water and made alkaline by the addition of ammonia solution. The

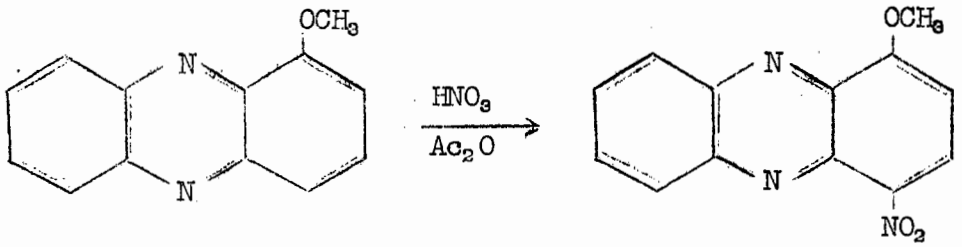
precipitated yellow product was filtered off, washed and dried. Crude 1-methoxy-4-nitrophenazine of melting point 215° - 220° was obtained in the theoretical yield (8.5 gms.).

Recrystallised from alcohol, 6 gms. of yellow needles of melting point 224° - 226° were obtained. Further recrystallisations raised the melting point to 225° - 226°.

Analysis:		C	H	N
$C_{13}H_9N_3O_3$	requires	61.15%	3.55%	16.46%
	Found	60.70%	3.30%	16.02%.

Crystals of 1-methoxy-4-nitrophenazine have a dirty yellow fluorescence. 1-Methoxy-4-nitrophenazine dissolves in concentrated hydrochloric acid to give a red solution from which it is precipitated on dilution.

(ii)



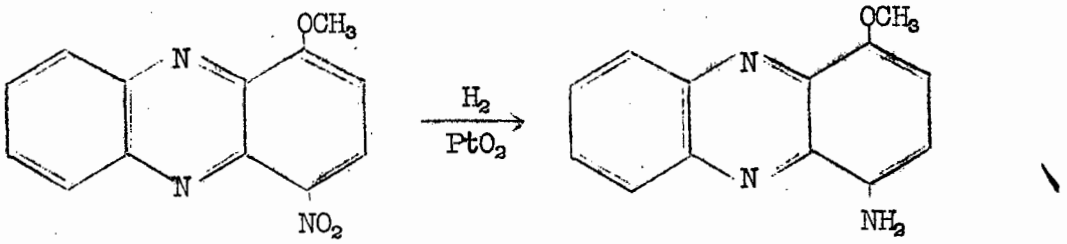
To 1 gm. of 1-methoxyphenazine, in 15 ml. of acetic anhydride, a solution of 4 ml. of fuming nitric acid (S.G. 1.5) in 10 ml. of acetic anhydride was slowly added with stirring at -8°. On completion of the addition, the reaction mixture was allowed to stand for 5 hours, the temperature rising to 3° during this period.

The reaction mixture was then poured into 100 ml. of water, made alkaline by the addition of ammonia solution and the precipitated product filtered off, washed and dried. 1-Methoxy-4-nitrophenazine was isolated by vacuum sublimation of the precipitate, extracting the sublimate with alcohol and recrystallising the extracted product from alcohol. 0.3 Gms. (25%) of 1-methoxy-4-nitrophenazine of

melting point 219° - 222° was obtained.

A mixed melting point with the previously prepared 1-methoxy-4 -nitrophenazine gave no depression of the melting point.

Preparation of 1-methoxy-4-aminophenazine.



2 Gms. of 1-methoxy-4-nitrophenazine were hydrogenated in 200 ml. of glacial acetic acid, in the presence of 0.4 gms. of Adam's catalyst, at 10 lbs. per sq. in., until the solution was almost colourless. The catalyst was filtered off and the yellowish filtrate shaken in air to oxidise the 9,10-dihydro-1-methoxy-4-aminophenazine to 1-methoxy-4-aminophenazine.

The dark red filtrate was diluted to 500 ml., made alkaline by the gradual addition of ammonia solution, maintaining the temperature below 25° by cooling in ice, stirring vigorously and the precipitated purple product filtered off, washed and dried. 1.1 Gms. of crude 1-methoxy-4-aminophenazine of melting point 210° - 212° were obtained.

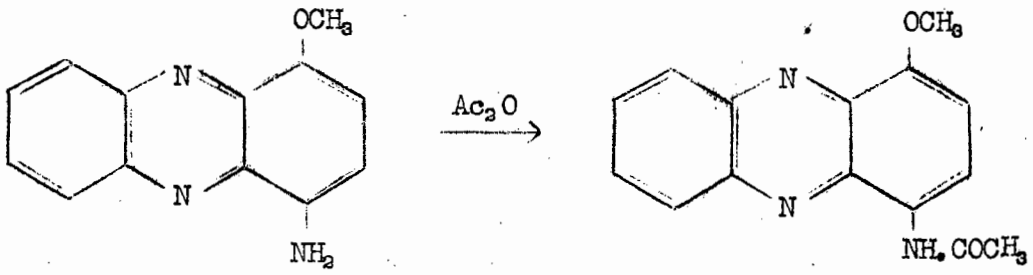
Recrystallised from petroleum ether (b. pt. 80° - 100°) 0.7 gms. (40%) of 1-methoxy-4-aminophenazine of melting point 210° - 212° was recovered. On repeated recrystallisation the melting point remained constant at 211° - 213°.

Analysis:	C	H	N
$C_{13}H_{11}N_3O$ requires	69.31%	4.92%	18.66%
Found	69.30%	4.65%	18.60%.

The purplish needles of 1-methoxy-4-aminophenazine obtained on recrystallisation have no fluorescence. Dissolved in concentrated

hydrochloric acid a red solution is obtained which turns yellowish on dilution.

Preparation of 1-methoxy-4-acetamidophenazine.



200 Mgm. of 1-methoxy-4-aminophenazine were treated with 3 ml. of acetic anhydride and after standing for 12 hours, occasionally swirling and crushing the lumps, poured into 60 ml. of water. The precipitated orange-yellow product was filtered off, washed and dried. 200 Mgm. of crude 1-methoxy-4-acetamidophenazine of melting point 227° - 232° were obtained.

Recrystallised from alcohol, 160 mgm. (67%) of bright orange needles of melting point 232° - 233° were obtained. This melting point remained unchanged on further recrystallisations.

Analysis:		C	H	N
$C_{15}H_{13}N_3O_2$	requires	67.41%	4.90%	15.72%
	Found	67.00%	4.86%	15.54%.

1-Methoxy-4-acetamidophenazine has an orange-red fluorescence and dissolves in concentrated hydrochloric acid to give a purple solution which turns brown on dilution.

Attempted conversion of 1-methoxy-4-aminophenazine to 1,4-dihydroxyphenazine.

(i) Unchanged 1-methoxy-4-aminophenazine was recovered on refluxing 0.5 gms. of 1-methoxy-4-aminophenazine with 25 ml. of 3 N sulphuric acid for 6 hours.

(ii) 0.5 Gms. of 1-methoxy-4-aminophenazine was refluxed with 35 ml. of 3 N sulphuric acid for 14 hours. After cooling, the solution was made alkaline by the addition of sodium hydroxide solution and filtered. The filtrate was neutralised by the addition of acetic acid. An extremely small amount of precipitate was isolated; not even enough for a melting point.

(iii) Compare H. Otomasu. Pharm. Bull. Japan 2, 283 (1954).

(a) 1.2 Gms. of 1-methoxy-4-aminophenazine were heated at 180° for 8 hours with 20 ml. of 25% hydrochloric acid. After cooling the reaction mixture was diluted once, made alkaline by the addition of sodium hydroxide solution and filtered. The purplish filtrate was just acidified with acetic acid, the precipitate filtered off, washed and dried. This orange-red material had a melting point of 165° - 168°.

On sublimation of this material a bright red sublimate, of melting point 167° - 175°, was collected at 8.5×10^{-3} mm. and a maximum temperature of 130°, followed by a purplish sublimate, of melting point 174° - 180°, collected at the same pressure at temperatures rising to 220°.

1,4-Dihydroxyphenazine obtained by Otomasu had a melting point of 230°.

(b) Acetylation of this product:- The combined sublimates of above, totalling 90 mgm., were dissolved in 3.0 ml. of dry pyridine, 1.3 ml. of acetic anhydride added and left to stand for 3 days. The greater part of the pyridine was removed under reduced pressure, water added and the precipitated yellow product filtered off, washed and dried. A melting point of 135° - 175° was recorded for this product.

Recrystallised from alcohol, dirty yellow crystals of melting point 176° - 188° were obtained. Recrystallised again the melting point rose to 179° - 195°.

The melting point of 1,4-diacetoxyphenazine is given[44] as 193.5° - 194°.

Conversion of 1-methoxy-4-aminophenazine to 1,4-dihydroxyphenazine and thence to 1,4-diacetoxyphenazine has not been accomplished, judging from the melting points of the products obtained.

Attempted demethylations of 1-methoxy-4-nitrophenazine.

(i) 1 Gm. of 1-methoxy-4-nitrophenazine was heated with 25 ml. of 48% hydrobromic acid at 110° - 120°, for periods of ½ hour, 3 hours and 4 hours. On cooling, in each case, the reaction mixture was poured into a solution of 40 gms. of sodium acetate crystals in 220 ml. of water and the precipitated product filtered off, washed and dried.

This product could not be purified by recrystallisation or by vacuum sublimation and was not alkali soluble. A positive result was obtained for a Lassaigne halogen test on this product.

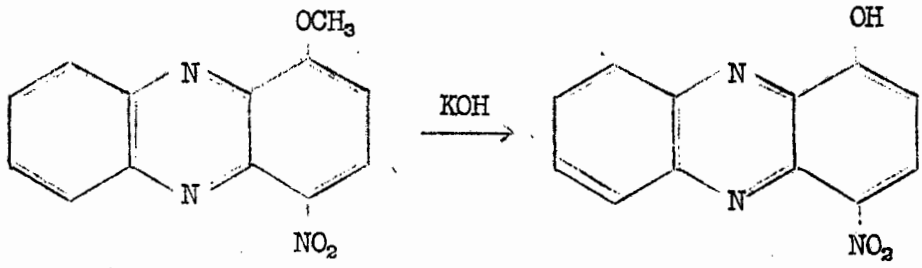
(ii) 1-Methoxy-4-nitrophenazine was refluxed with 10% hydrobromic acid for 1 hour. On precipitation of the product by the addition of sodium acetate, only unchanged starting material was isolated.

(iii) 0.5 Gms. of 1-methoxy-4-nitrophenazine was heated with 12.5 ml. of 48% hydrobromic acid and 12.5 ml. of glacial acetic acid at 120° for 1¼ hours. On slight dilution of the reaction mixture

a reddish precipitate separated. The reaction mixture was neutralised, the precipitate filtered off, washed and dried. This product could not be recrystallised or vacuum sublimed and was not alkali soluble.

(iv) An unsuccessful attempt to demethylate 0.5 gms. of 1-methoxy -4-nitrophenazine was made by refluxing in 40 ml. of dry benzene with 0.9 gms. of anhydrous aluminium chloride.

Preparation of 1-hydroxy-4-nitrophenazine.



Demethylation of 1-methoxy-4-nitrophenazine was effected by refluxing 3.3 gms. of 1-methoxy-4-nitrophenazine for 1 hour with 330 ml. of 10% potassium hydroxide solution and 330 ml. of alcohol. A deep red solution was obtained soon after refluxing was started. The alcohol was distilled off and the reaction mixture cooled. On cooling, red silky needles of the potassium salt of 1-hydroxy-4-nitrophenazine, which on heating appeared to decompose at approximately 350°, separated. 3.6 Gms. of this product were obtained.

Without separation of the crystals, the reaction mixture was diluted and 6 N hydrochloric acid slowly added with vigorous stirring until the solution was neutral. The separated yellow product was filtered off, well washed and dried. (In some cases, a further small precipitate of 1-hydroxy-4-nitrophenazine could be obtained by adding a little hydrochloric acid to the washings, if they were red).

The yield of crude 1-hydroxy-4-nitrophenazine, of melting point 179° - 181°, was 2.5 gms. This was recrystallised from petroleum

ether (b. pt. 80° - 100°) to give 2 gms. (64%) of yellow to greenish needles of 1-hydroxy-4-nitrophenazine of melting point 187° - 189°. Better looking crystals, and a more favourable volume of solvent to weight of compound, were obtained using petroleum ether (b. pt. 120° - 180°) as solvent for recrystallisation.

Analysis:		C	H	N
$C_{12}H_7N_3O_3$	requires	59.74%	2.93%	17.42%
	Found	59.30%	2.85%	17.30%

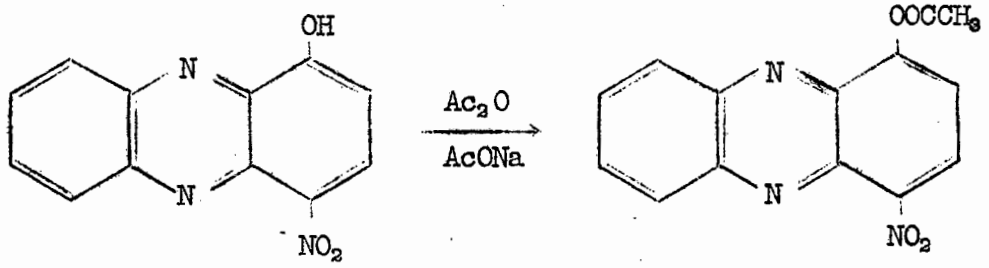
1-Hydroxy-4-nitrophenazine dissolves in alkali and in concentrated hydrochloric acid to give red solutions. On diluting the acidic solution the compound precipitates. On dissolving 1-hydroxy-4-nitrophenazine in acetone a yellow solution is obtained which turns red on adding water. Dissolved in hydroxylic solvents such as methanol and ethanol reddish solutions were obtained. In a non-hydroxylic solvent, such as cyclohexane, a yellow solution is obtained. The yellow crystals on exposure to the atmosphere turn slightly red and have a reddish fluorescence.

It was found that aqueous solutions of the potassium salt of 1-hydroxy-4-nitrophenazine gave coloured precipitates with a large number of cations, especially those of the transition elements. The following were recorded:

Cation	Colour of precipitate
Mg^{++}	Red
Ti^{+++}	Orange
Va^{++}	Brownish
Mn^{++}	Dark
Fe^{+++}	Brown-red
Co^{++}	Red
Ni^{++}	Dark green
Cu^{++}	Dark blue
Zn^{++}	Red
Mo^{6+}	Red
Ag^{+}	Black
Ce^{+++}	Red

Hg_2^{++}	Black
Pb^{++}	Red
UO_2^{++}	Red

Preparation of 1-acetoxy-4-nitrophenazine.

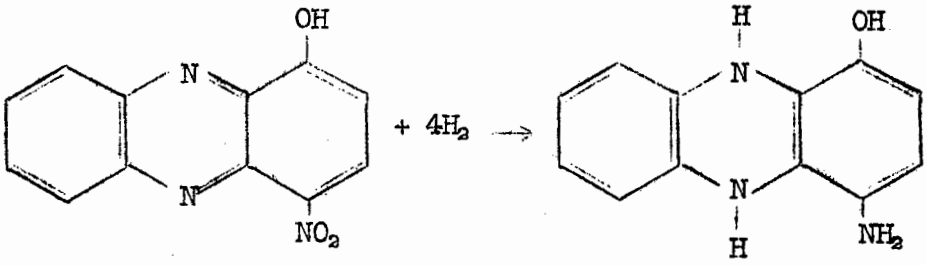


0.5 Gms. of 1-hydroxy-4-nitrophenazine was refluxed for 1 hour with 5 ml. of acetic anhydride and 1 gm. of fused sodium acetate. After cooling the reaction mixture was diluted and the precipitated product filtered off, washed and dried. The yield of crude 1-acetoxy -4-nitrophenazine of melting point 183° - 189° was approximately 550 mgm. (94%). This was recrystallised from alcohol to a melting point of 187° - 190°. Recovery was 450 mgm. Subsequent recrystallisations did not alter the melting point.

Analysis:		C	H	N
$C_{14}H_9N_3O_4$	requires	59.34%	3.20%	14.84%
	Found	59.9%	3.71%	15.0%

These fine, very light yellow needles of 1-acetoxy-4-nitrophenazine have no noticable fluorescence. Dissolved in concentrated hydrochloric acid a golden red solution, which rapidly turns red, is obtained. It is very rapidly hydrolysed by boiling with dilute alkali to give a red solution.

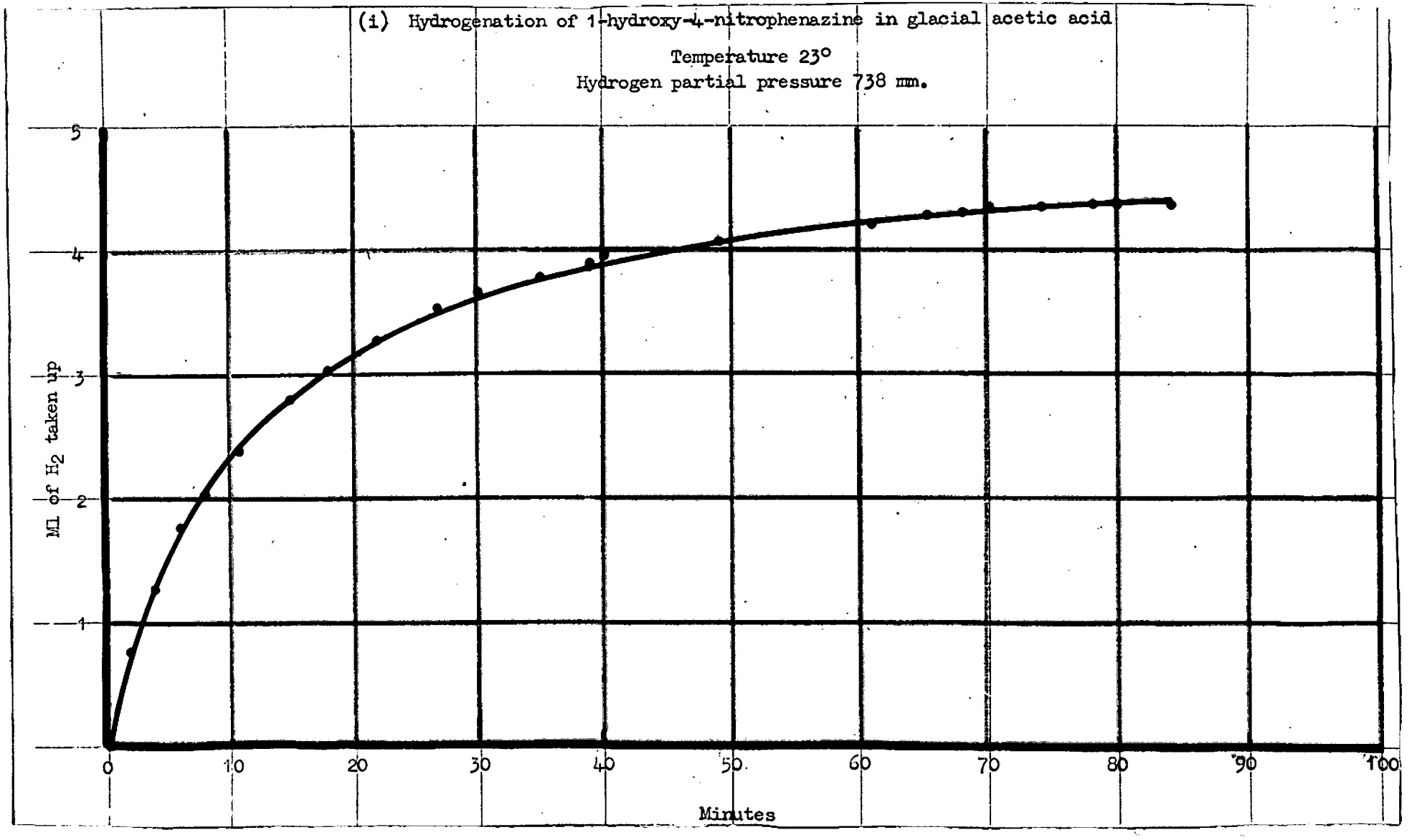
Quantitative hydrogenation of 1-hydroxy-4-nitrophenazine.



(i) Hydrogenation of 1-hydroxy-4-nitrophenazine in glacial acetic acid

Temperature 23°

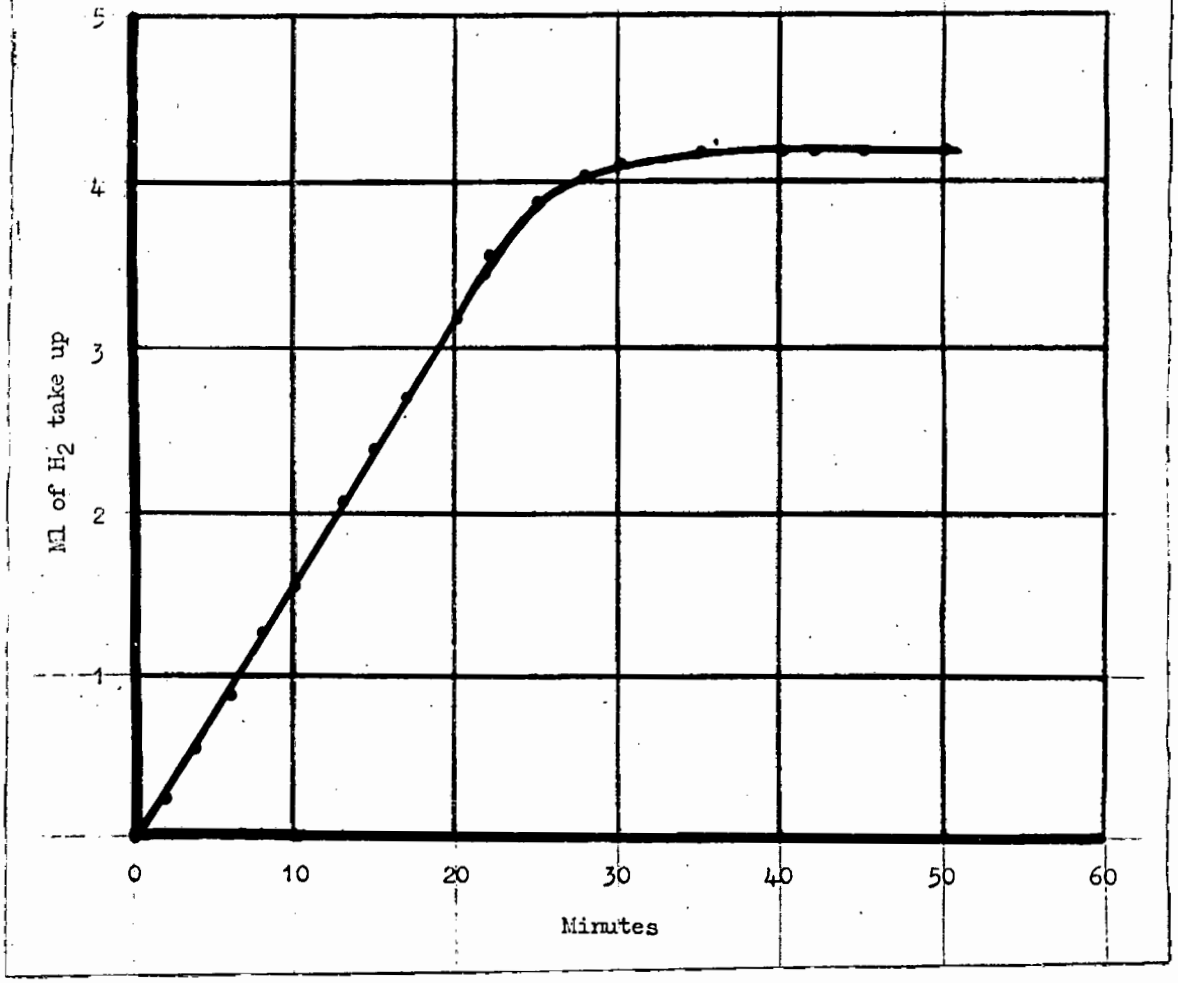
Hydrogen partial pressure 738 mm.



(ii) Hydrogenation of 1-hydroxy-4-nitrophenazine in dilute NaOH

Temperature 22°

Hydrogen partial pressure 733.6 mm.



(i) Glacial acetic acid as solvent.

10 Mgm. of 1-hydroxy-4-nitrophenazine were hydrogenated in 5 ml. of glacial acetic acid in the presence of 2 mgm. of Adam's catalyst and the volume of hydrogen taken up with time recorded.

From the curve of hydrogen uptake with time, it is seen that the hydrogenation is complete after approximately 70 minutes. The volume of hydrogen taken up at N.T.P., 3.873 ml., agrees with the calculated volume, 3.718 ml., for 4 moles of hydrogen per molecule of 1-hydroxy-4-nitrophenazine, for the conversion to 9,10-dihydro-1-hydroxy-4-aminophenazine.

(ii) Dilute sodium hydroxide solution as solvent.

10.03 Mgm. of 1-hydroxy-4-nitrophenazine were dissolved in 5 ml. of 0.1% sodium hydroxide solution and hydrogenated in the presence of 2 mgm. of Adam's catalyst, recording the volume of hydrogen taken up with time.

Volume of hydrogen taken up at N.T.P.	3.744 ml.
Theoretical hydrogen uptake	3.726 ml.

From the curve of hydrogen uptake with time it is seen that hydrogenation is complete after approximately 30 minutes.

From the above results it is seen that the hydrogenation of 1-hydroxy-4-nitrophenazine is almost twice as rapid with dilute sodium hydroxide solution as solvent, as with glacial acetic acid as solvent.

Attempted preparation of 1-hydroxy-4-aminophenazine.

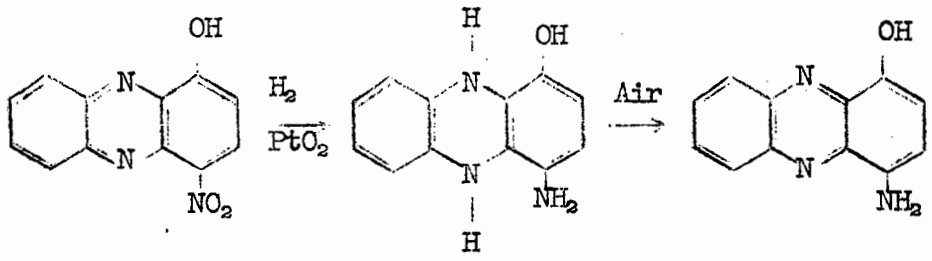
0.5 Gms. of 1-hydroxy-4-nitrophenazine was hydrogenated in 150 ml. of glacial acetic acid in the presence of 0.1 gms. of Adam's catalyst at 10 lbs. per sq. in. for 80 minutes. The catalyst was filtered off and the almost colourless filtrate shaken up in the air to oxidise the

9,10-dihydro-1-hydroxy-4-aminophenazine. The filtrate was diluted, and while chilling, neutralised with ammonia solution and then extracted with ether. After drying the ether over anhydrous sodium sulphate it was evaporated. A purplish residue, which dissolved in concentrated hydrochloric acid to give a dark red solution, but did not dissolve in alkali, remained.

On attempting to recrystallise this residue from ethyl acetate, amorphous looking material separated and more separated from the cold mother liquor on standing. Neither of these products could be redissolved in ethyl acetate. The crude material gave a purple alcoholic solution, which, after standing for a day, lost its colour and deposited an amorphous sediment.

No melting point could be determined and this product could not be recrystallised or alkali extracted.

Preparation of 1-hydroxy-4-aminophenazine.

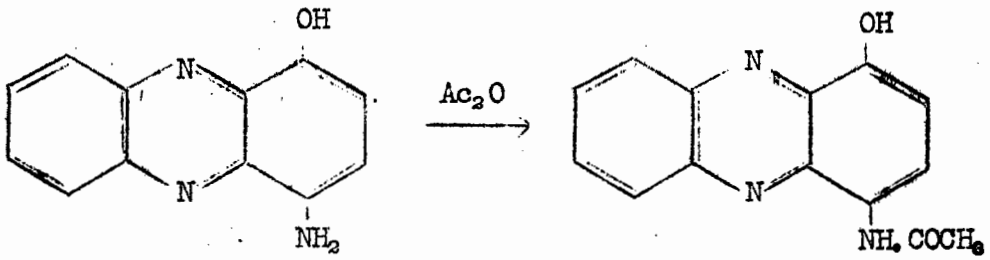


1 Gm. of 1-hydroxy-4-nitrophenazine was hydrogenated in 260 ml. of a 0.15% sodium hydroxide solution, in the presence of 0.1 gms. of Adam's catalyst at 10 lbs. per sq. in., until the solution was practically colourless. (Palladium-charcoal was equally effective as the catalyst). The catalyst was filtered off from the solution and the filtrate shaken up in the air to oxidise the 9,10-dihydro-1-hydroxy-4-aminophenazine to 1-hydroxy-4-aminophenazine. The filtrate, which turned blue on oxidation, was neutralised by the addition of a little glacial acetic acid, the precipitated 1-hydroxy-4-amino-phenazine filtered off, washed and dried in vacuo over calcium chloride.

0.55 Gms. (63%) of crude 1-hydroxy-4-aminophenazine was isolated. On very rapid heating this crude compound melted at approximately 188° with decomposition. On slower heating it was found to melt at 190° - 194° with subsequent resolidification.

On attempted recrystallisation of the crude product from organic solvents, it decomposed. Recrystallised from water, small purplish needles were obtained in small quantity, but these apparently decomposed on keeping for a short period.

Preparation of 1-hydroxy-4-acetamidophenazine.



500 Mgm. of crude 1-hydroxy-4-aminophenazine were crushed fine, thoroughly mixed with 12.5 ml. of acetic anhydride and left to stand at room temperature for 9 hours. The reaction mixture was then poured into 200 ml. of water and the precipitated product filtered off, washed and dried. 500 Mgm. of crude 1-hydroxy-4-acetamidophenazine (m. pt. 215° - 217°) were obtained.

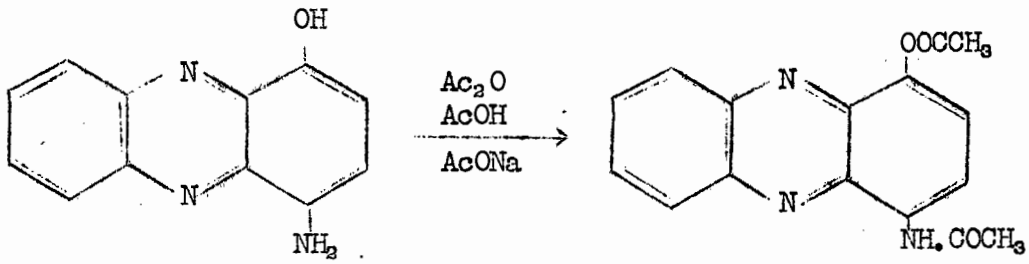
Recrystallised from toluene, purplish heavy needles were obtained. After four recrystallisations, by which time the yield had dropped to 50 mgm., the melting point was constant at 226.5° - 227.5°.

Analysis:		C	H	N
$C_{14}H_{11}N_3O_2$	requires	66.37%	4.38%	16.60%
	Found	66.60%	4.34%	16.03%

1-Hydroxy-4-acetamidophenazine has a faint dark red fluorescence. Dissolved in 5% sodium hydroxide a deep wine coloured solution is obtained.

Preparation of 1-acetoxy-4-acetamidophenazine.

(i)



1 Gm. of 1-hydroxy-4-nitrophenazine was hydrogenated as before. Immediately the hydrogenation was stopped a little glacial acetic acid was added. A white precipitate of 9,10-dihydro-1-hydroxy-4-amino-phenazine separated, was filtered off and dried in vacuo over calcium chloride.

About three quarters of this precipitate, which darkened after a few hours, was shaken up in 10 ml. of glacial acetic acid to oxidise completely any 9,10-dihydro compound present. 20 Ml. of acetic anhydride and 2 gms. of fused sodium acetate were added and then refluxed for 30 minutes. After cooling, the reaction mixture was poured into water, the precipitated yellow product filtered off, washed and dried. A practically quantitative yield of crude 1-acetoxy -4-acetamidophenazine was obtained. On heating, this product showed some melting at 190° and melted completely at 200° - 205°.

Recrystallised from alcohol bright yellow needles, which melt slightly at 190° and completely at 205° - 210°, were obtained. The melting point of this compound is slightly dependent on the rate of heating, being lower the more rapid the rate of heating.

Analysis:		C	H	N
$C_{16}H_{13}N_3O_3$	requires	65.09%	4.44%	14.23%
	Found	64.42%	4.42%	14.28%

1-Acetoxy-4-acetamidophenazine has a bright yellow fluorescence. 1-Acetoxy-4-acetamodophenazine dissolves in concentrated hydrochloric acid to give a red solution from which it is precipitated on dilution.

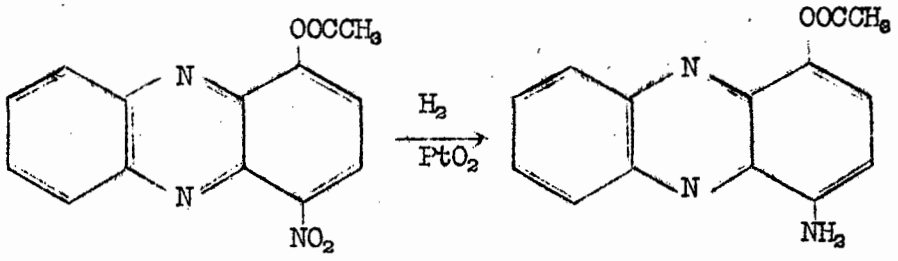
On boiling with dilute hydrochloric acid, the compound is rapidly hydrolysed to give a wine coloured solution. Boiled with dilute alkali it is rapidly hydrolysed to give a purple solution.

(ii) Heating 1-hydroxy-4-aminophenazine with acetic anhydride for a few minutes also gave 1-acetoxy-4-acetamidophenazine.

(iii) 0.5 Gms. of 1-hydroxy-4-nitrophenazine was hydrogenated in a solution of 0.2 gms. of sodium hydroxide in 50 ml. of water. This solution was poured into a nitrogen filled flask, chilled in ice. A little crushed ice, followed by 1 ml. of acetic anhydride, was added with vigorous stirring. A pale green precipitate formed almost immediately. The reaction mixture was left to stand for 30 minutes and the precipitate then filtered off, washed and dried. An almost quantitative yield of crude 1-acetoxy-4-acetamidophenazine of melting point 199° - 208° was obtained.

After a few recrystallisations from alcohol bright yellow needles, showing signs of melting from 192° and melting rapidly at 205° - 210°, were obtained. A mixed melting point with previously prepared 1-acetoxy-4-acetamidophenazine gave no depression of the melting point.

Preparation of 1-acetoxy-4-aminophenazine.



(i) 500 Mgm. of 1-acetoxy-4-nitrophenazine were hydrogenated, at 10 lbs. per sq. in. in 30 ml. of glacial acetic acid, in the presence of approximately 70 mgm. of Adam's catalyst. The

catalyst was filtered off from the practically colourless solution and the filtrate shaken in the air to oxidise the 9,10-dihydro-1-acetoxy-4-aminophenazine to 1-acetoxy-4-aminophenazine, the solution turning red. After slight dilution, the solution was neutralised by the gradual addition of 6 N sodium hydroxide, stirring vigorously and cooling. The precipitated product was filtered off, washed, dried and found to have a melting point of 143° - 153°.

After three recrystallisations from petroleum ether (b. pt. 80° - 100°) the melting point remained unchanged at 166.5° - 169°. The recovery was extremely poor.

Analysis:		C	H	N
$C_{14}H_{11}N_3O_2$	requires	66.37%	4.38%	16.59%
	Found	66.62%	4.42%	16.10%.

These wine coloured needles of 1-acetoxy-4-aminophenazine have no fluorescence. Dissolved in concentrated hydrochloric acid a yellow solution is obtained turning greenish on dilution. Heating with dilute hydrochloric acid rapidly hydrolyses the compound, the solution turning brown. Hot dilute alkali and cold concentrated ammonia solutions readily hydrolyse the compound, judging from the blue solution which rapidly develöpes.

(ii) This preparation was repeated and sodium bicarbonate used to neutralise the acid solution. A crude product, which could be purified only by vacuum sublimation to give a small amount of 1-acetoxy-4-aminophenazine, was obtained.

Attempted preparations of 1,4-dihydroxyphenazine from 1-hydroxy-4-aminophenazine.

(i) (a) 0.55 Gms. of crude 1-hydroxy-4-aminophenazine was refluxed with 17 ml. of 3 N sulphuric acid for 16 hours. After

cooling, the reaction mixture was diluted to about 120 ml. and sodium acetate added to precipitate the product (pH 5 - 6). The precipitate was filtered off, washed and dried.

On rapid heating, this crude product melted at 155° with almost immediate resolidification and finally melted at 230° with decomposition. 0.5 Gms. of crude product were obtained.

Vacuum sublimation of this product gave a deep red sublimate, which on heating was found to melt at 181° - 183° with subsequent resolidification; finally melted, with decomposition, at 231° - 233°. 0.35 Gms. of sublimate were obtained.

This product, dissolved in acid gave a red solution, in alkali a blue solution and in acetone a purple solution.

(b) 0.2 Gms. of the above sublimed product, 0.3 gms. of freshly fused sodium acetate and 10 ml. of acetic anhydride were refluxed for 1½ hours. The reaction mixture was poured into 130 ml. of water and the yellow precipitate filtered off, washed and dried. 0.2 Gms. of material with a melting point of 155° - 158° were obtained.

After three recrystallisations from alcohol the melting point was 168° - 185°. After a further recrystallisation from cyclohexane the melting point was 168° - 193°. On heating, melting was generally slow, until about 190° when relatively rapid melting set in.

From the melting points of the above two products it was evident that pure compounds had not been obtained.

(c) 100 Mgm. of the sublimed product were dissolved in 3.3 ml. of dry pyridine, 1.5 ml. of acetic anhydride

added and allowed to stand at room temperature for 25 hours. The pyridine was removed at low temperature under reduced pressure, the residual 2 - 3 ml. diluted with water and the precipitated yellow product filtered off, washed and dried. 50 Mgm. of a precipitate of melting point 169° - 180° were obtained.

Recrystallised from alcohol and then from benzene the melting point was 172° - 180°. On recrystallisation from alcohol, two types of crystals were observed, light yellow and dark yellow needles. After slow growing of the crystals, the larger golden needles were handpicked from the mixture and found to have a melting point of 191° - 194°. A mixed melting point with 1,4-diacetoxyphenazine, prepared later, gave no depression of the melting point.

The light yellow crystals remaining showed signs of melting at 173° and melted relatively rapidly at 183° - 195°. On recrystallisation from alcohol these crystals showed slight signs of melting at 174°, slightly increasing in rate of melting at 187°, fairly rapidly at 198° - 199° and melting was complete at 203°.

From the results of the above preparations (a), (b) and (c) it is evident that 1,4-dihydroxyphenazine was not the only compound isolated after refluxing 1-hydroxy-4-aminophenazine with 3 N sulphuric acid for 17 hours.

The final melting point (230°) of the product isolated, on treating 1-hydroxy-4-aminophenazine as above, agreed with that of 1,4-dihydroxyphenazine[57], but there was also the temporary melting point at 181° - 183°, similar to that observed for 1-hydroxy-4-aminophenazine (191° - 194°). The light yellow crystals left in the acetylated product after removal of the 1,4-diacetoxyphenazine were found to have a

melting point, (174°) 187° - 203°, not dissimilar to that of 1-acetoxy-4-acetamidophenazine, (190°) 205° - 210°.

These light yellow crystals on hydrolysis by heating with dilute alkali and with dilute acid showed similar colour changes to 1-acetoxy-4-acetamidophenazine, but different from those of 1,4-diacetoxyphenazine.

Apparently incomplete conversion of 1-hydroxy-4-amino-phenazine to 1,4-dihydroxyphenazine took place under the above conditions, and therefore on acetylation both 1,4-di-acetoxyphenazine and 1-acetoxy-4-acetamidophenazine were formed. Unfortunately, due to lack of material, no nitrogen analysis, which could have supported this theory, could be done.

(ii) (a) 1-Hydroxy-4-aminophenazine was treated as above and the product vacuum sublimed. A deep red sublimate, obtained at approximately 0.5 mm. and a maximum temperature of 120°, on heating showed signs of subliming at 170° and melted with resolidification at 180° - 183°. The sublimate coming over at the same pressure at a temperature of 120° - 145° was found, on heating, to show signs of subliming at 160°, melted with resolidification at 180° - 183° and finally melted at 230°. Heating in a sealed tube did not alter these observations, other than suppressing the sublimation.

Recrystallised from petroleum ether (b. pt. 120° - 180°) the product had a melting point of 180° - 185° only.

Analysis:		C	H
$C_{12}H_8N_2O_2$	requires	67.92%	3.80%
	Found	69.0%	4.30%.

This product is not 1,4-dihydroxyphenazine .

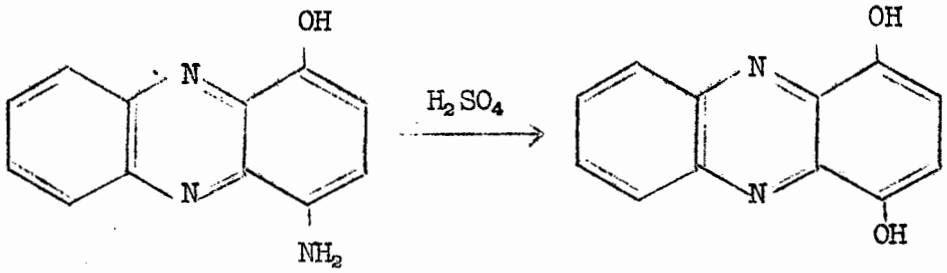
(b) 30 Mgm. of the above recrystallised material were dissolved in 1.5 ml. of dry pyridine, 1 ml. of acetic anhydride added and left to stand for a day. The greater part of the pyridine was removed at low temperature under reduced pressure. Water was added to the residue, the precipitated product filtered off, washed and dried. This crude precipitate had a melting point of 178° - 198°. Recrystallised from alcohol the melting point was 183° - 204°. Subsequent recrystallisation did not improve the melting point.

Analysis:		C	H
$C_{16}H_{12}N_2O_4$	requires	64.86%	4.09%
	Found	64.01%	4.73%

Judging from the melting points of this preparation, (ii), recrystallisation of the product from the acid treatment removes the greater part of the 1,4-dihydroxyphenazine.

(iii) 1,4-Dihydroxyphenazine was not obtained on heating 1-hydroxy -4-aminophenazine with 3N phosphoric acid, at 150°, for 36 hours.

Preparation of 1,4-dihydroxyphenazine.



Approximately 550 mgm. of freshly precipitated crude 1-hydroxy -4-aminophenazine were heated with 30 ml. of 3 N sulphuric acid at 148° for 17 hours. After cooling, the reaction mixture was slightly diluted and neutralised with 6 N sodium hydroxide, keeping the temperature from rising above 25°.

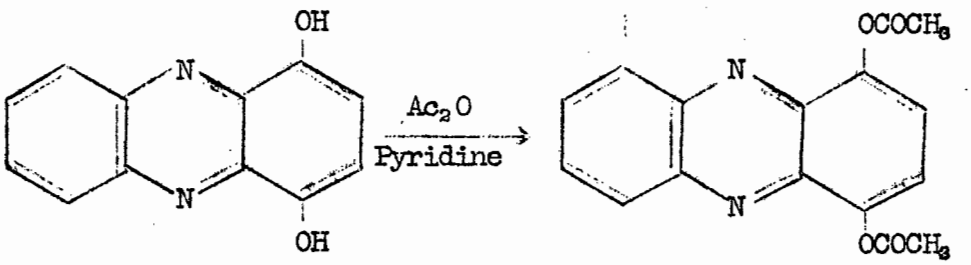
The precipitate was filtered off, well washed, dried and vacuum sublimed. During the sublimation the temperature was allowed to rise slowly to a maximum of 185° at approximately 7 x 10^{-2} mm. A bright red sublimate of melting point 228° - 231°, showing slight signs of melting at 225°, was obtained in a 70 mgm. (13%) yield.

Analysis:	C	H	N
$C_{12}H_8N_2O_2$ requires	67.92%	3.80%	13.20%
Found	67.85%	3.79%	13.07%.

1,4-Dihydroxyphenazine dissolves in dilute alkali and in hydrochloric acid to give bluish solutions.

The sublimate was recrystallised from chloroform to give bright red needles of melting point 234° - 236°, softening at 230°. Further recrystallisations did not alter the melting point.

Preparation of 1,4-diacetoxyphenazine.



40 Mgm. of 1,4-dihydroxyphenazine were dissolved in 3.2 ml. of dry pyridine, 1 ml. of acetic anhydride added and after vigorous shaking allowed to stand in a stoppered test tube for about 90 hours. The reaction mixture was then heated for 45 minutes on a waterbath at 55° and the pyridine removed at this temperature under reduced pressure.

Water was added to the residue and the precipitated dark yellow product filtered off, washed and dried. A good yield of crude 1,4-diacetoxyphenazine (m. pt. 185° - 193°) was obtained.

On recrystallisation from alcohol in the presence of a little norite and cooling rapidly, fine yellow needles of melting point 193° - 195°, softening at 185° separated. Recrystallised again the melting point was 193° - 196° with softening at 190°.

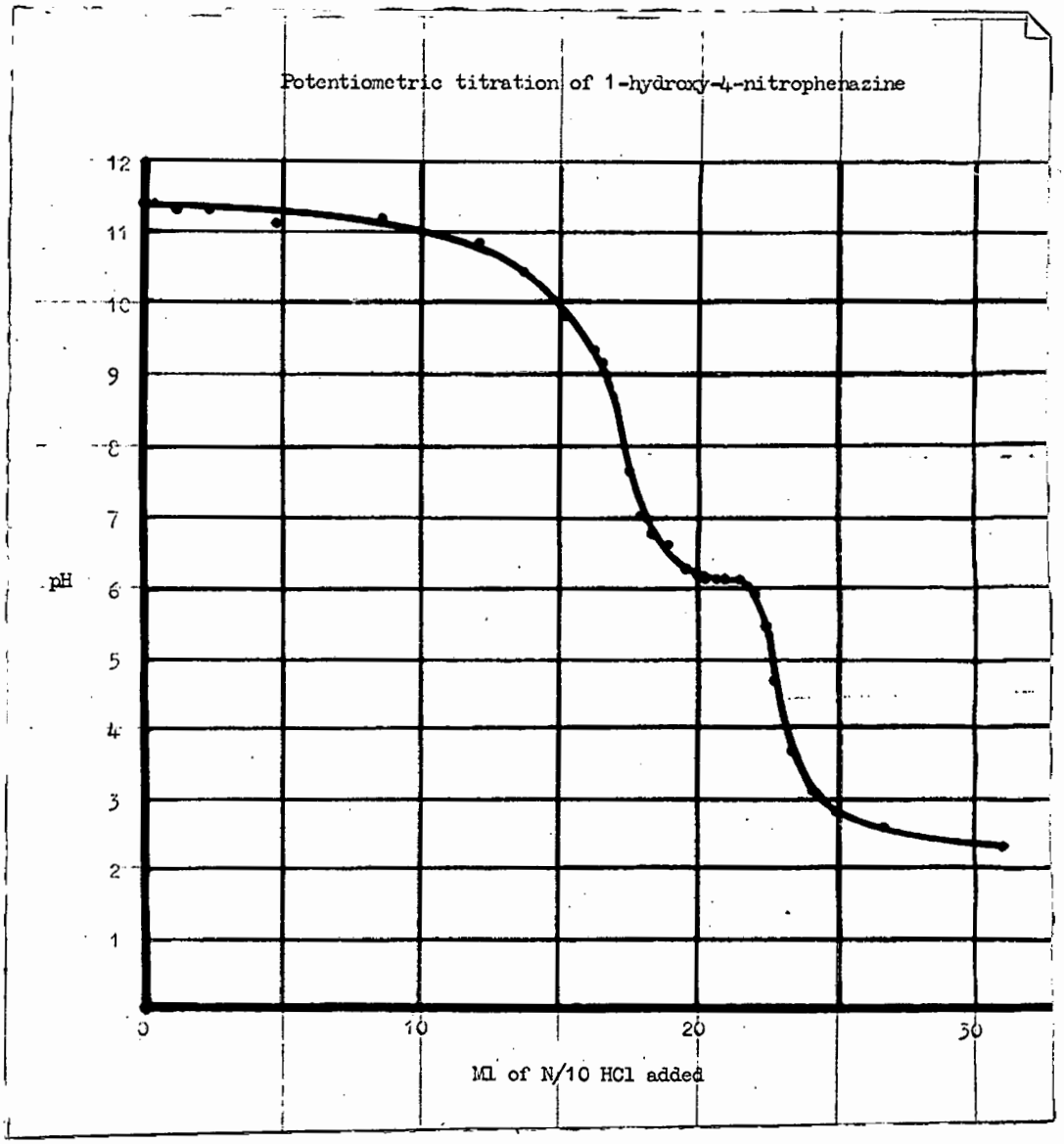
Analysis:		C	H	N
$C_{16}H_{12}N_2O_4$	requires	64.86%	4.08%	9.46%
	Found	64.90%	4.22%	9.17%.

1,4-Diacetoxyphenazine has a yellow fluorescence. Dissolved in concentrated hydrochloric acid a gold brown solution is obtained becoming lighter on dilution. 1,4-Diacetoxyphenazine is rapidly hydrolysed by boiling with dilute acid or dilute alkali, blue solutions being obtained.

In order to obtain further evidence that nitration of 1-methoxyphenazine had given only one product, 1-methoxy-4-nitrophenazine, and not a mixture of isomers:

(i) All compounds described in the 1,4-substituted series of phenazines were subjected to paper chromatography. The following solvents were used.
   (a) Butanol: conc. HCl = 2:1 saturated with water solution.
   (b) Butanol: conc. HCl = 4:1 saturated with water solution.
   (c) Butanol: conc. HCl = 8:1 saturated with water solution.
   (d) Butanol: water: acetic acid = 5:4:1 solution.
   (e) Butanol saturated with N hydrochloric acid, by downward flow.

   In no case did a particular compound show more than a single


Potentiometric titration of 1-hydroxy-4-nitrophenazine
pH
12
11
10
9
8
7
6
5
4
3
2
1
0
10
20
30
Ml of N/10 HCl added

spot after development for as long as was practicable with the length of paper used (‡ 30 cm.).

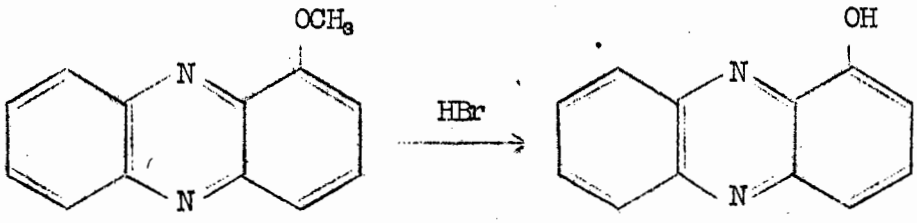
(ii) A polarographic reduction of 1-methoxy-4-nitrophenazine in anhydrous formic acid was done by Dr. T. Pinfold. From the resulting polarogram the presence of only one compound was indicated.

(iii) A potentiometric titration of 1-hydroxy-4-nitrophenazine in dilute alkali was done. A quantity of 1-hydroxy-4-nitrophenazine was dissolved in approximately 25 ml. of N/10 sodium hydroxide and titrated with approximately N/10 hydrochloric acid. The change in pH with volume of acid added was recorded.

1-Hydroxy-4-nitrophenazine is precipitated from a pH of about 7 down. From the figure of change of pH with volume of hydrochloric acid added it is seen that there is only one plateau and therefore the presence of only one compound is indicated.

Preparation of 1-hydroxyphenazine.

A.R. Surrey. Org. Syn. 26, 87.



A 61% yield of 1-hydroxyphenazine of melting point 152° - 154° was obtained.

Instead of the last ethereal extraction, as described by Surrey, the precipitate could be filtered off, washed, dried and then recrystallised. A product in comparable yield and purity was obtained by this shorter route.

1-Hydroxyphenazine has a slight yellow fluorescence, dissolved in concentrated hydrochloric acid a wine coloured solution is obtained and in alkali a purple solution.

Attempted nitration of 1-hydroxyphenazine.

1.4 Gms. of potassium nitrate were added, with stirring, to a solution of 1 gm. of 1-hydroxyphenazine in 15 ml. of concentrated sulphuric acid, cooled to approximately -5°. Stirring was continued for 3 hours and the reaction mixture then left to stand for 13 hours, the temperature eventually rising to 5°. The reaction mixture was poured into water, the greater part of the acid neutralised and the precipitated product filtered off, washed and dried. 1 Gm. of crude product, melting at 170° - 175° with decomposition, was obtained.

Recrystallised from petroleum ether (b. pt. 120° - 180°) in the presence of a little norite, a heterogeneous looking product, which on heating showed signs of melting from 180° and melted rapidly with

decomposition at 202° - 205°, was obtained. Further recrystallisations did not improve the appearance or the melting point of this product.

From paper chromatograms of this product, compared with 1-hydroxyphenazine and 1-hydroxy-4-nitrophenazine, using the following solvents:

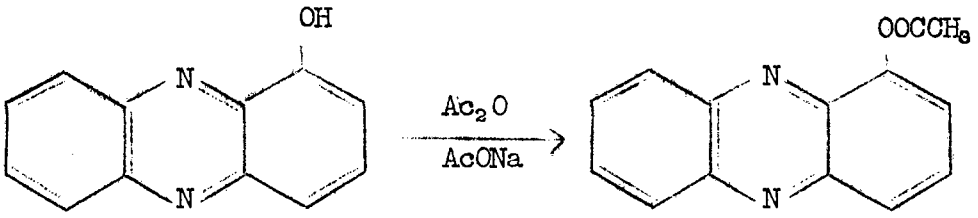
(i) Butanol : water : acetic acid = 5 : 4 : 1.

(ii) Butanol : conc. hydrochloric acid = 4 : 1 saturated with water, and

(iii) Butanol saturated with concentrated ammonia solution, it appeared that some 1-hydroxy-4-nitrophenazine and some unchanged 1-hydroxyphenazine were present in the recrystallised product.

Preparation of 1-acetoxyphenazine.

I. Yoshioka and Y. Kidani. J. Pharm. Soc. Japan, 72, 1301 (1952)



Recrystallised from petroleum ether (b. pt. 80° - 100°) 50% of the theoretical yield of 1-acetoxyphenazine of melting point 119° - 121° was obtained.

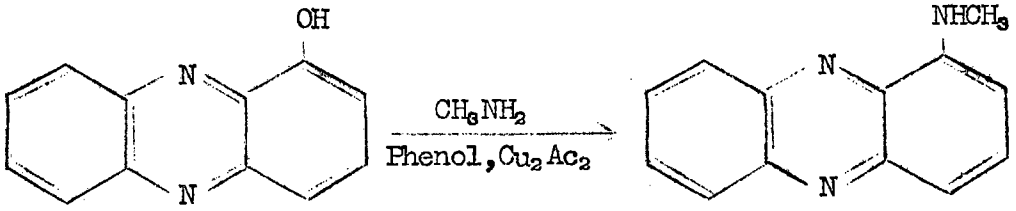
These irregular light yellow crystals have a slight yellow fluorescence and dissolve in concentrated hydrochloric acid to give a brown red solution. Heated with dilute hydrochloric acid 1-acetoxyphenazine is rapidly hydrolysed to give a red solution. Heated with dilute alkali it is rapidly hydrolysed to give a purple solution.

Attempted nitration of 1-acetoxyphenazine.

(i) Unchanged 1-acetoxyphenazine was recovered on adding to 0.7 gm. of 1-acetoxyphenazine in 15 ml. of acetic anhydride a solution of 6 ml. of fuming nitric acid (S.G. 1.5) in 6 ml. of acetic anhydride, and allowing to stand overnight at 0°.

(ii) To a suspension of 2 gms. of 1-acetoxyphenazine in 25 ml. of acetic anhydride at -5°, 10 ml. of fuming nitric acid (S.G. 1.5) was added extremely slowly with vigorous stirring. The temperature was then allowed to rise slowly to room temperature and the reaction mixture left to stand for 12 hours. On pouring the reaction mixture into water a black tar precipitated and could not be solidified or extracted to give anything but black tarry residues.

Conversion of 1-hydroxyphenazine to 1-methylaminophenazine.



0.5 Gms. of 1-hydroxyphenazine, 0.03 gms. of cupric acetate, 5 gms. of phenol and about 15 ml. of methylamine were heated together at 150° - 170°, for 7 hours in a sealed tube. After cooling the reaction mixture was diluted and filtered. Phenol and unchanged 1-hydroxyphenazine passed through in the alkaline filtrate.

The tarry residue was taken up in ether, the ether evaporated and the residue dried in vacuo over calcium chloride. The tarry residue was triturated with 5 N hydrochloric acid, filtered, the filtrate slightly diluted and made just alkaline. The separated red precipitate was filtered off, washed, dried and found to have a melting point of 138° - 146°.

After four recrystallisations from alcohol : water (1 : 3) solution, the melting point was constant at 149° - 151°. Due to the darkness of the melt it was not easy to decide on the melting range. Only about 50 - 60 mgm. (10%) of 1-methylaminophenazine were recovered after two recrystallisations.

Analysis:	C	H	N
$C_{13}H_{11}N_3$ requires	74.63%	5.26%	20.08%
Found	74.12%	5.31%	19.52%.

The red needles of 1-methylaminophenazine have a bright orange red fluorescence. Dissolved in concentrated hydrochloric acid a yellow-green solution, passing through green and blue-green to blue on dilution, is obtained.

A more convenient method for the isolation of the 1-methylaminophenazine was, to make the reaction mixture strongly acid, by the addition of hydrochloric acid after cooling and exhaustively extracting with ether to remove the phenol. The residue was then made alkaline again and the precipitated 1-methylaminophenazine filtered off.

Attempted conversion of 1-hydroxyphenazine to 1-dimethylaminophenazine.

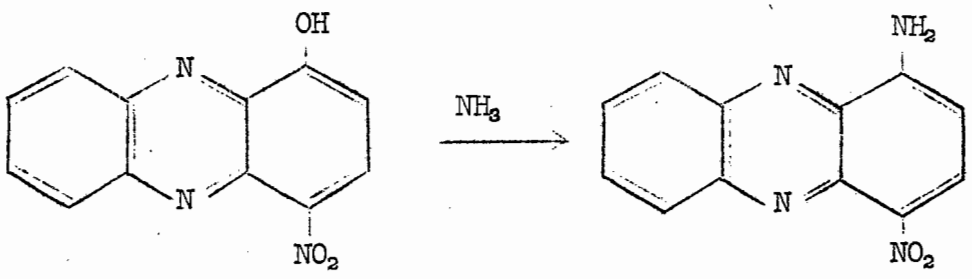
1-Hydroxyphenazine could not be converted to 1-dimethylaminophenazine by heating 0.5 gms. of 1-hydroxyphenazine, 0.03 gms. of cupric acetate, 5 gms. of phenol and 12 ml. of dimethylamine in a sealed tube at (i) 160° for 7 hours, or
(ii) 130° - 140° for 8 hours.

Attempted conversion of 1-hydroxy-4-nitrophenazine to 1-methylamino-4-nitrophenazine.

0.5 Gms. of 1-hydroxy-4-nitrophenazine was heated in a sealed tube at 160° - 165° for 7 hours with 5 gms. of phenol, 0.03 gms. of cupric acetate and approximately 20 ml. of methylamine.

A dark tarry product and a small amount of unchanged 1-hydroxy-4-nitrophenazine were isolated.

Conversion of 1-hydroxy-4-nitrophenazine to 1-amino-4-nitrophenazine.



0.5 Gm. of 1-hydroxy-4-nitrophenazine was heated for 7 hours at 110° - 130° with 40 ml. of alcohol and 40 ml. of concentrated ammonia solution in a sealed tube. The reaction mixture was cooled and then evaporated to about half its original volume.

After cooling the red precipitate in the reaction mixture was filtered off, washed until the washings were colourless and dried. 0.27 Gms. of crude 1-amino-4-nitrophenazine (m. pt. 224° - 227°) was obtained and recrystallised from butanol. 0.22 Gms. (44%) were recovered, with a melting point of 247° - 249°. A mixed melting point with a sample of prepared 1-amino-4-nitrophenazine gave no depression of the melting point.

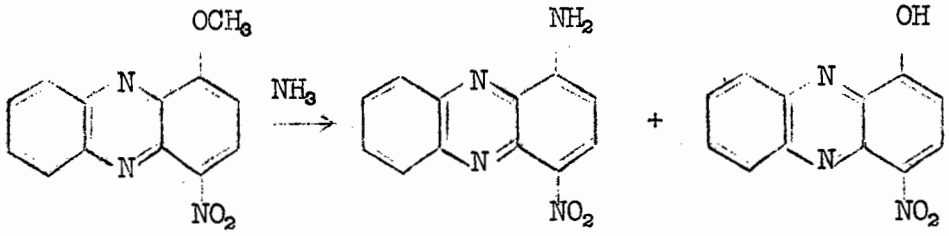
From the combined filtrate and washings 0.1 gms. of unchanged 1-hydroxy-4-nitrophenazine (m. pt. 186° - 188°) was isolated by neutralising with 6 N hydrochloric acid, filtering off the precipitate, washing and drying. After recrystallisation from petroleum ether (b. pt. 80° - 100°) no depression of the melting point was observed on admixture with the starting material.

Attempted conversion of 1-methoxy-4-nitrophenazine to 1-amino-4-nitrophenazine.

0.5 Gm. of 1-methoxy-4-nitrophenazine was heated at 200° for

4 hours with 30 ml. of alcohol and 30 ml. of concentrated ammonia solution in a sealed tube. On cooling only charred looking material, of indefinite melting point, insoluble in acid, was isolated.

Conversion of 1-methoxy-4-nitrophenazine to 1-amino-4-nitrophenazine.



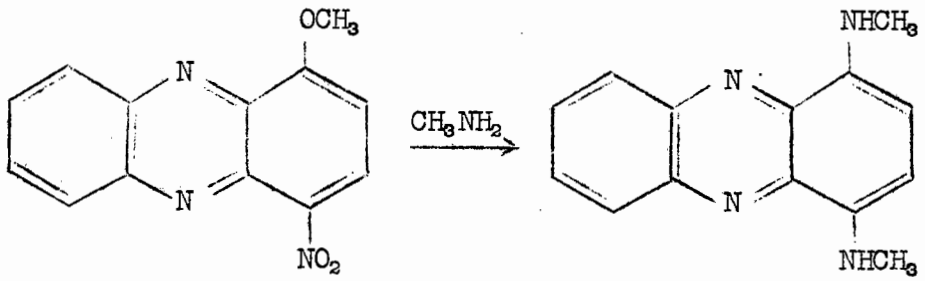
1 Gm. of 1-methoxy-4-nitrophenazine was heated in a sealed tube with 75 ml. of alcohol and 75 ml. of concentrated ammonia solution at 110° - 130° for 5 hours. The reaction mixture was cooled over a period of about 2 - 3 hours and the greater part of the alcohol and ammonia then removed by evaporation to about half of its original volume.

The mixture was cooled, filtered and the red precipitate well washed, combining the washings with the filtrate. After drying the precipitate 0.4 gms. (43%) of crude 1-amino-4-nitrophenazine (m. pt. 219° - 225°) was obtained. Recrystallised from butanol the melting point rose to 249°- 251°. A mixed melting point of this compound with 1-amino-4-nitrophenazine gave no depression of the melting point.

The combined filtrate and washings were just neutralised by the addition of 6 N hydrochloric acid and the yellow precipitate which separated filtered off, washed, dried and found to have a melting point of 178° - 180°. 0.2 Gms. of this product with melting point 186° - 188° was recovered on recrystallisation from petroleum ether (b. pt. 80° - 100°). A mixed melting point of this product with 1-hydroxy-4-nitrophenazine gave no depression of the melting point.

Reaction of 1-methoxy-4-nitrophenazine with an aqueous alcoholic solution of methylamine.

(i)



This was an attempt to prepare 1-methylamino-4-nitrophenazine.

0.5 Gms. of 1-methoxy-4-nitrophenazine was heated with 40 ml. of alcohol and 40 ml. of 33% aqueous methylamine in a sealed tube at 110° - 130° for 7 hours.

On cooling a purplish solution containing some solid matter, had resulted. This was filtered, the filtrate slightly diluted and evaporated to about half volume, to remove the greater part of the alcohol and methylamine. The residue was cooled and a purplish product which had separated was filtered off, washed, dried and found to have a melting point of approximately 130°. Nothing separated from the filtrate on neutralisation.

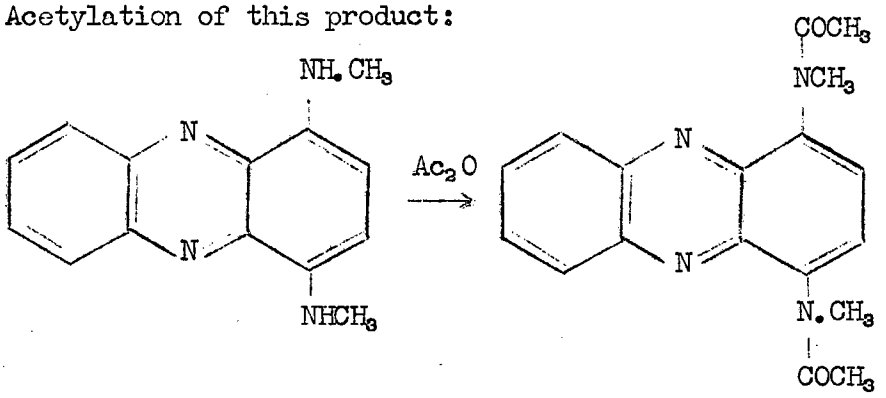
This product was recrystallised from petroleum ether (b. pt. 80° - 100°) to give small irregular dark blue needle-like crystals with melting point 135° - 140°. The melting point was constant at 135° - 140°, with decomposition, after two recrystallisations.

Analysis:	C	H	N
Found	70.2%	5.53%	23.8%.

This analysis was found to agree with that required if 1,4-dimethylamino-phenazine was the product.

	C	H	N
$C_{14}H_{14}N_4$ requires	70.53%	5.92%	23.51%.

(ii) Acetylation of this product:



Approximately 400 mgm. of 1,4-dimethylaminophenazine were treated with about 15 ml. of acetic anhydride and 10 ml. of dry pyridine and left to stand at room temperature for a day. After standing for some time the reaction mixture clears, and after standing for a further period, orange needles separate. The reaction mixture was poured into water, the precipitated product filtered off, washed, dried and found to melt at 210° - 216°.

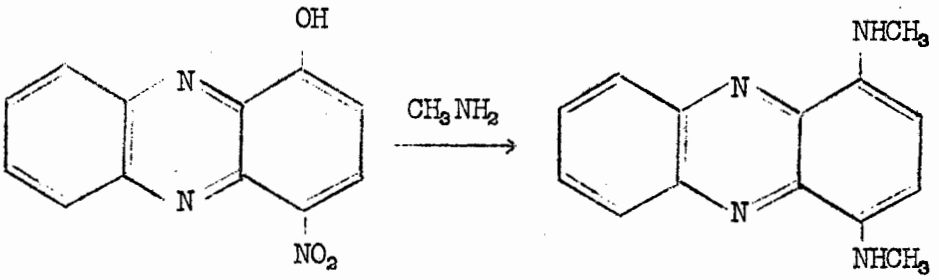
After three recrystallisations from xylene the orange needles of 1,4-di-methylacetamidophenazine had a melting point of 236° - 239°. The recovery was extremely small.

Analysis:		C	H	N
$C_{18}H_{18}N_4O_2$	requires	67.05%	5.62%	17.38%
	Found	66.34%	5.36%	18.12%.

1,4-Di-methylacetamidophenazine has a yellow fluorescence. Dissolved in concentrated hydrochloric acid a wine coloured

solution is obtained, turning lighter on dilution. Boiled in dilute hydrochloric acid a brownish solution is obtained.

Reaction of 1-hydroxy-4-nitrophenazine with an aqueous-alcoholic methylamine solution.



0.5 Gms. of 1-hydroxy-4-nitrophenazine was heated at 120° - 130° for 7 hours with 35 ml. of alcohol and 35 ml. of 33% aqueous methylamine solution in a sealed tube. The reaction mixture was allowed to cool slowly, chilled and the separated fine purplish needles filtered off, washed and dried in vacuo over calcium chloride.

On heating the crystals begin shrinking at 120° and melt at 125° - 127° with resolidification. Recrystallised from petroleum ether (b. pt. 80° - 100°) the crystals had a melting point of 134° - 138°. Recrystallised again the melting point was 134° - 138° with shrinking at 128°. On admixture with a sample of previously prepared 1,4-di-methylaminophenazine no depression of the melting point was observed.

On attempting to recrystallise this product from aqueous-alcoholic solutions it decomposed. The originally blue solutions passed through purple, with time, to brown and a lot of amorphous sediment separated. A cold alcoholic solution of 1,4-di-methylaminophenazine decomposes gradually, as was determined by spectrophotometric observation. Dissolved in hydrochloric acid a red solution is obtained.

The crystals on exposure to the atmosphere lose their blue colour, becoming black amorphous and insoluble in petroleum ether.

Kept in a concentrated sulphuric acid : sodium hydroxide desiccator, no change in the melting point was observed after two months.

Reaction of 1-methoxy-4-nitrophenazine with aqueous-alcoholic dimethylamine.

0.5 Gms. of 1-methoxy-4-nitrophenazine was heated at approximately 120° for 7 hours with 25 ml. of 25% aqueous dimethylamine solution and 30 ml. of alcohol in a sealed tube. Hydrolysis of the 1-methoxy-4-nitrophenazine to 1-hydroxy-4-nitrophenazine by the dimethylamine in the cold, was evident by the fact that the solution turned red.

After cooling the reaction mixture was slightly diluted and boiled down to about half the original volume to remove the greater part of the alcohol and dimethylamine. A black mixture resulted, was cooled, filtered and the black residue washed and dried. It did not melt below 360° and could not be purified.

Attempted conversion of 1-hydroxyphenazine to 1-aminophenazine with aqueous-alcoholic ammonia solution.

Unchanged 1-hydroxyphenazine was recovered on heating 0.5 gms. of 1-hydroxyphenazine with 30 ml. of alcohol and 35 ml. of concentrated ammonia solution in a sealed tube at 110° - 130° for 7 hours.

Attempted conversion of 1-hydroxyphenazine to 1-methylaminophenazine.

A sample of 1-hydroxyphenazine was heated with a 33% w/w solution of methylamine in alcohol, for 5 - 6 hours at 110° - 140° in a sealed tube. After cooling, the solvent was evaporated off to leave a dark tarry residue. The residual dark charred looking material after trituration with ether had a melting point of 88° - 91° but could not be purified by recrystallisation or vacuum sublimation.

Attempted conversion of 1-methoxyphenazine to 1-methylaminophenazine.

Unchanged 1-methoxyphenazine was recovered on heating 0.5 gms. of 1-methoxyphenazine with 50 ml. of a 30% w/w alcoholic solution of methylamine for 5 hours at 110° - 130° in a sealed tube.

Preparation of iso-amylnitrite.

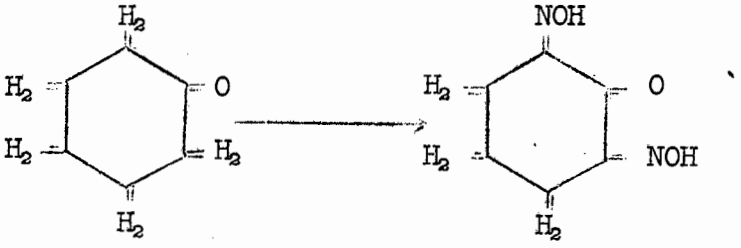
W.A. Noyes. Org. Syn. 16, 7.

$$C_5H_{11}OH + HNO_2 \xrightarrow[H_2SO_4]{} C_5H_{11}NO_2.$$

A 90% yield of iso-amylnitrite of boiling point 96° - 98° was obtained.

Preparation of bishydroxyimino-cyclohexanone.

Compare W. Borsche Chem. Zentr. 1549 (1909) II.



This synthesis was not fully described by Borsche and therefore the preparation, as conducted, is described.

40 Gms. of cyclohexanone were placed in a 500 ml. wide mouth conical flask surrounded by an ice-salt freezing mixture. When the temperature of the cyclohexanone had dropped to -6° a total of 120 ml. of isoamylnitrite and 8.0 ml. of acetylchloride were added in fractions, with vigorous mechanical stirring, maintaining the temperature below 0° throughout. These additions were effected by adding first 20 ml. of isoamylnitrite followed by 1.3 ml. of acetylchloride and then repeating the procedure until the total additions had been made. The total time taken for the additions was approximately 30 hours.

On completion of the additions the reaction mixture was stirred for a further hour and the separated white crystals then filtered off and sucked dry. 47 Gms. (74%) of crude bishydroxyiminocyclo-hexanone, which melted at 208° with decomposition, were obtained.

These crystals could not be satisfactorily recrystallised from methanol, due to apparent decomposition.

(Unless the additions, as described, were not made extremely slowly, the temperature of the reaction mixture rapidly rose to above 100° in a few seconds, resulting in a dark tarry decomposed mixture).

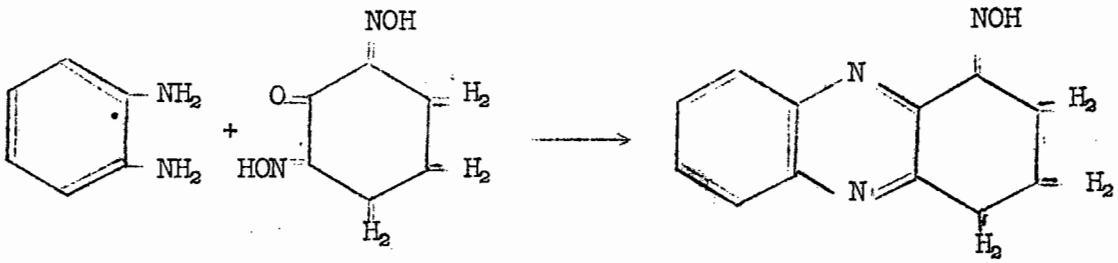
Bishydroxyiminocyclohexanone dissolved in sodium hydroxide solution to give a yellow solution, darkening in colour to red with increasing sodium hydroxide concentration. On adding Brady's reagent to an aqueous solution of bishydroxyiminocyclohexanone a deep yellow precipitate was obtained.

Attempted new preparation of bishydroxyiminocyclohexanone.

To 20 gms. of cyclohexanone, in a 250 ml. conical flask, 370 ml. of 10 N hydrochloric acid (14 gms. of HCl) were added. This was placed in a freezing mixture and while maintaining the internal temperature below 0°, 26.5 gms. of sodium nitrite were slowly added, in portions, over a period of 2 hours with vigorous stirring. The reaction mixture was left overnight at 0° and then filtered. Yellowish crystals, accompanied by a large amount of sludge, were obtained. These crystals showed no definite melting point and could not be recrystallised.

Preparation of 1-hydroxyimino-1,2,3,4-tetrahydrophenazine.

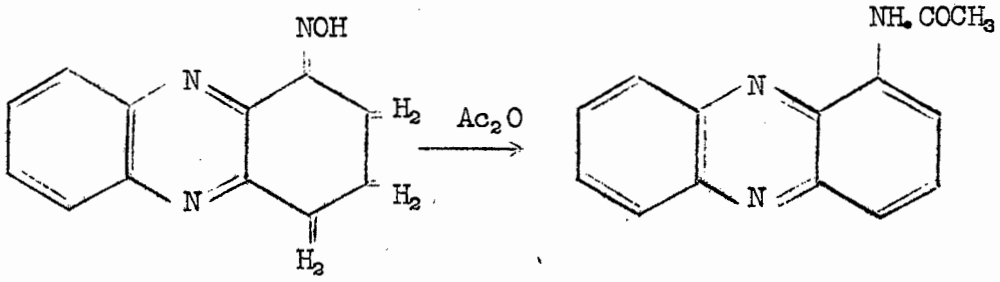
G.H. Cookson. J.C.S. 1328 (1953).



Crude unrecrystallised bishydroxyiminocyclohexanone was used for this preparation. A 54% yield of 1-hydroxyimino-1,2,3,4-tetrahydrophenazine, melting at 218° with brisk effervesence, was obtained.

Preparation of 1-acetamidophenazine.

G. H. Cookson. J. C. S. 1328 (1953).

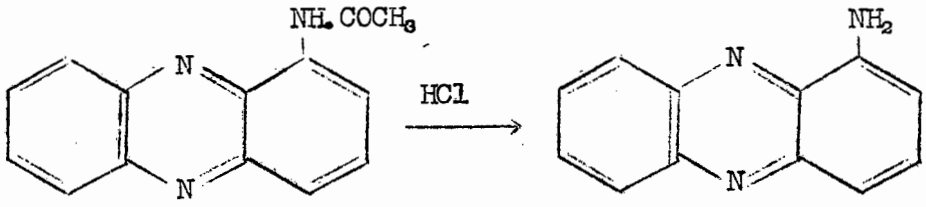


A 52% yield of crude 1-acetamidophenazine (m. pt. 154° - 162°) was obtained. Recrystallised from methanol golden yellow needles of melting point 167° - 170° were recovered in 44% yield. Yields varied between 30% and 50%.

1-Acetamidophenazine crystals have a strong yellow fluorescence; also in chloroform solution. Dissolved in concentrated hydrochloric acid a wine coloured solution is obtained.

Preparation of 1-aminophenazine.

G. H. Cookson. J. C. S. 1328 (1953).



1-Aminophenazine (m. pt. 178° - 180°) was obtained in 67% yield.

The dark red needles have a very slight red fluorescence. In concentrated hydrochloric acid a yellow-green solution is obtained, passing through green to blue on dilution.

Attempted conversions of 1-aminophenazine to 1-hydroxyphenazine.

(i) 0.5 Gms. of 1-aminophenazine, 0.03 gms. of cupric acetate, 5 gms. of phenol and 25 ml. of water were heated at 140° - 160° for 7½ hours in a sealed tube and then allowed to cool.

The reaction mixture was made strongly acid, extracted with ether to remove the phenol, then made alkaline, filtered and the filtrate neutralised. No precipitate was obtained.

(ii) No 1-hydroxyphenazine was obtained on repeating (i) using only 0.5 ml. of water. A dirty amorphous precipitate of indefinite melting point, which could not be extracted with acid or alkali was obtained.

(iii) 1 Gm. of 1-aminophenazine was dissolved in 70 ml. of concentrated sulphuric acid, cooled to -8° and 0.38 gms. of sodium nitrite added very slowly with stirring. After standing for 15 minutes the solution was poured into 500 ml. of water and left to stand for a few hours. The solution was neutralised and the separated precipitate filtered off, washed and dried. This precipitate had no definite melting point and could not be recrystallised or vacuum sublimed.

(iv) 1 Gm. of 1-aminophenazine was dissolved in 70 ml. of glacial acetic acid. To this solution at approximately 18° a solution of nitrosyl sulphuric acid, (prepared by dissolving 0.39 gms. of sodium nitrite in 90 ml. of slightly warmed concentrated sulphuric acid), was slowly added with stirring and the temperature of the reaction mixture slowly brought down to 8°.

0.5 Gms. of 1-aminophenazine, 2.5 gms. of sodium meta-bisulphite ($Na_2S_2O_5$) and 6 ml. of water were heated together, in a sealed tube at 148°, for 8 hours with occasional shaking. After cooling, the reaction mixture was made fairly strongly alkaline with 6 N sodium hydroxide solution. A purple colour developed and the smell of ammonia was noticeable. The alkaline mixture was boiled for about 30 minutes, cooled, filtered and the filtrate neutralised by the addition of hydrochloric acid and extracted with ether.

The ether extract was extracted with 3 N sodium hydroxide, this neutralised with hydrochloric acid and again extracted with ether. On evaporation of the ether an extremely small amount of 1-hydroxyphenazine was obtained. This was indicated to be 1-hydroxyphenazine by paper chromatograms when this compound moved similarly to 1-hydroxyphenazine and no separation of this compound from 1-hydroxyphenazine, when mixed, was found.

(a) Ethyl acetate : acetic acid : water = 11 : 6 : 4.

(b) Butanol : conc. hydrochloric acid = 4 : 1 saturated with water, and

(c) Butanol : conc. hydrochloric acid = 8 : 1 saturated with water were the solvents used, for the method of downward flow.

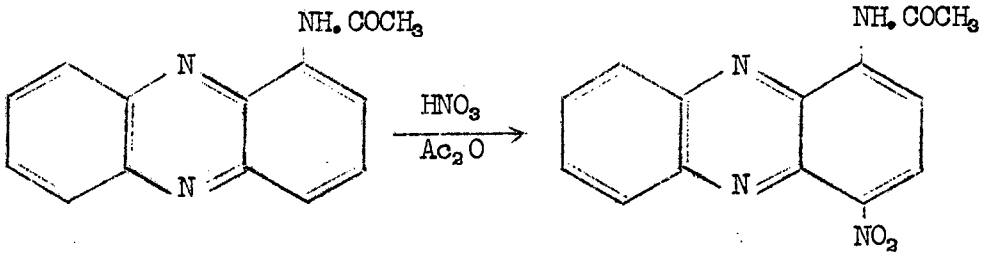
An appreciable amount of unchanged 1-aminophenazine, determined by paper chromatograms, using the same solvents, was found present in the first ethereal extract.

Attempted nitration of 1-acetamidophenazine.

(i) 1-Acetamidophenazine could not be nitrated at 6° in glacial acetic acid using concentrated nitric acid.

(ii) 1-Acetamidophenazine could not be nitrated in glacial acetic acid with concentrated nitric acid heating on a water-bath for 40 minutes.

Preparation of 1-acetamido-4-nitrophenazine.



To a suspension of 5 gms. of 1-acetamidophenazine in 75 ml. of acetic anhydride, was slowly added, with vigorous stirring, a solution of 17.5 ml. of fuming nitric acid in 50 ml. of acetic anhydride, maintaining the temperature at -3°. On completion of the addition the reaction mixture was left to stand at -3° to 0° for 10 hours.

The reaction mixture was then poured into 500 ml. of water, the precipitated yellow product filtered off, washed and dried. The yield of crude 1-acetamido-4-nitrophenazine of melting point 230° - 236° was 6.2 gms. (theoretical yield). On recrystallisation of this product the following changes in the melting point were observed.

1st recrystallisation m. pt. 241° - 245°
2nd recrystallisation m. pt. 260° - 263°
3rd recrystallisation m. pt. 272° - 274°.

After the third recrystallisation only 1.5 gms. (25%) of 1-acetamido -4-nitrophenazine were recovered. Further recrystallisations of this product raised the melting point to 273° - 275°.

Analysis:		C	H	N
$C_{14}H_{10}N_4O_3$	requires	59.55%	3.57%	19.85%
	Found	59.55%	3.43%	20.25%

1-Acetamido-4-nitrophenazine recrystallised from alcohol as

yellow needles with a yellow fluorescence. Dissolved in concentrated hydrochloric acid a red solution is obtained from which it is precipitated on dilution.

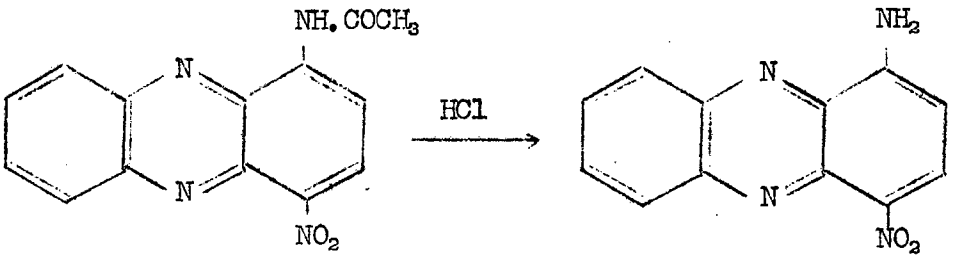
Recrystallisation of the crude 1-acetamido-4-nitrophenazine from acetone, raised the melting point much more rapidly, but the recovery was extremely poor.

1st recrystallisation from acetone m. pt. 259° - 262°
2nd recrystallisation from acetone m. pt. 274° - 276°.

Recrystallisation of the crude product from toluene did not change the melting point appreciably.

1st recrystallisation from toluene m. pt. 242° - 246°
2nd recrystallisation from toluene m. pt. 244° - 246°.

Preparation of 1-amino-4-nitrophenazine.



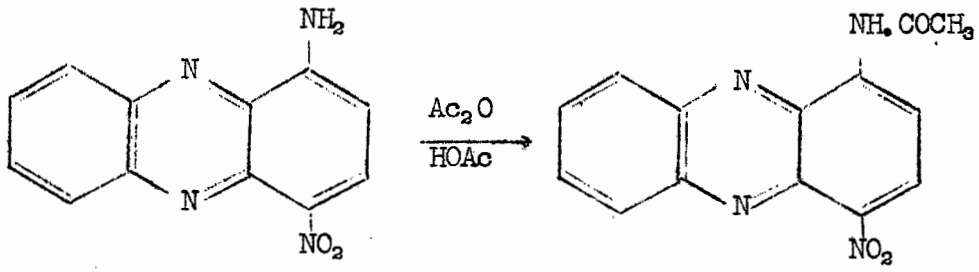
1 Gm. of 1-acetamido-4-nitrophenazine was boiled for 17 minutes with 70 ml. of concentrated hydrochloric acid and 120 ml. of water. After cooling, the dark blue solution was diluted with 100 ml. of water, made just alkaline by the addition of ammonia solution, the precipitated 1-amino-4-nitrophenazine filtered off, washed, dried and found to have a melting point of 218° - 221° with decomposition.

Recrystallised from butanol either dark, heavy, red needles, or finer lighter red needles, were obtained, depending on the rate of cooling. 1-Amino-4-nitrophenazine had a melting point of 249° - 251° after three recrystallisations when the recovery was 0.4 gms. (47%).

Analysis:		C	H	N
$C_{12}H_8N_4O_2$	requires	60.00%	3.33%	23.33%
	Found	60.00%	3.45%	22.6%

1-Amino-4-nitrophenazine has a bright dark red fluorescence. Dissolved in concentrated hydrochloric acid a blue solution is obtained which does not change in colour on dilution.

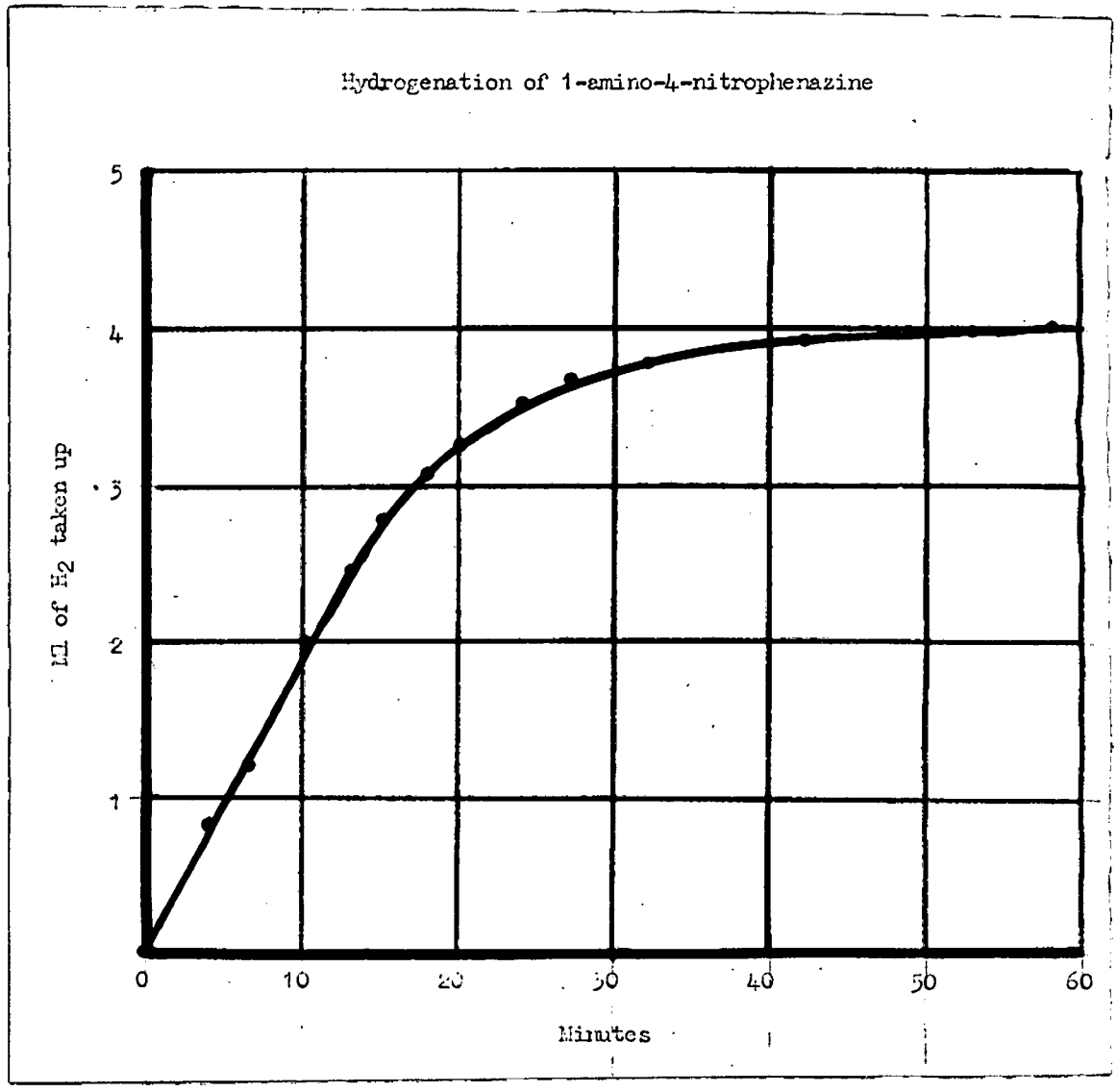
Acetylation of 1-amino-4-nitrophenazine.



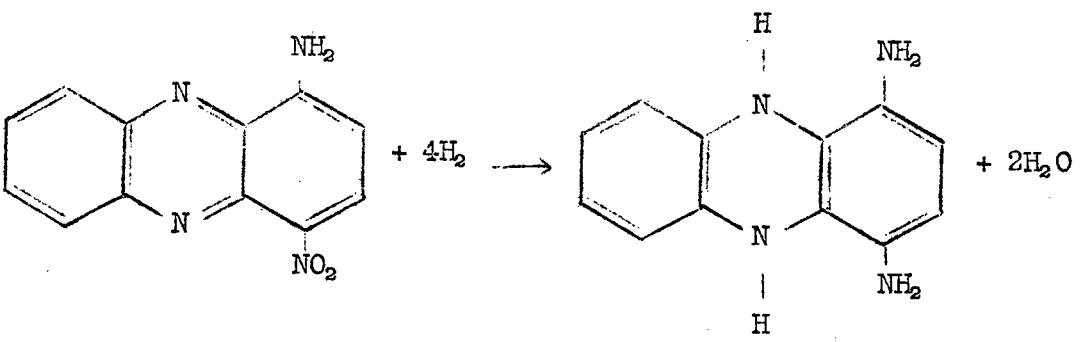
0.2 Gm. of 1-amino-4-nitrophenazine was boiled for 30 minutes with 10 ml. of acetic anhydride and 5 ml. of glacial acetic acid, poured into 100 ml. of cold water and the precipitated yellow 1-acetamido-4-nitrophenazine filtered off, washed and dried. Recrystallised from alcohol pure 1-acetamido-4-nitrophenazine of melting point 269° - 271° was obtained. No change in the melting point was observed on admixture with a sample of 1-acetamido-4 -nitrophenazine.

Attempted conversion of 1-amino-4-nitrophenazine to 1-hydroxy-4 -nitrophenazine by acid hydrolysis.

0.3 Gms. of 1-amino-4-nitrophenazine was refluxed with 20 ml. of 3 N sulphuric acid for 36 hours. The original blue solution changed to red-brown and a dark precipitate separated. The precipitate was filtered off, washed, dried but did not melt below 360° and could not be purified by recrystallisation or vacuum sublimation.


Hydrogenation of 1-amino-4-nitrophenazine
Ml of H_2 taken up
5
4
3
2
1
0
10
20
30
40
50
60
Minutes

Quantitative hydrogenation of 1-amino-4-nitrophenazine.



9.99 Mgm. of 1-amino-4-nitrophenazine were hydrogenated at atmospheric pressure in the presence of 2 mgm. of Adam's catalyst in 5 ml. of glacial acetic acid. From the figure illustrating hydrogen uptake with time it is seen that the hydrogenation is complete after 40 minutes. The hydrogen uptake corresponded to 4 mole of hydrogen per molecule of 1-amino-4-nitrophenazine which is equal to the theoretical amount required to convert 1-amino-4-nitrophenazine to 9,10-dihydro-1,4-diaminophenazine. On completion of the hydrogenation the original blue solution was almost colourless.

Attempted preparation of 1,4-diaminophenazine.

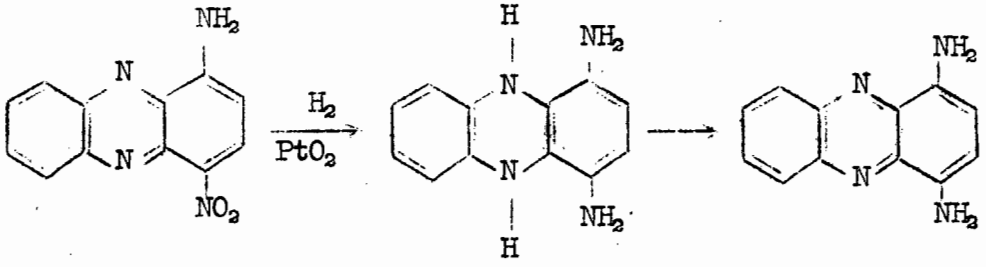
0.3 Gm. of 1-amino-4-nitrophenazine was hydrogenated in 40 ml. of glacial acetic acid in the presence of 0.06 gms. of Adam's catalyst at 30 lbs. per sq. in. The catalyst was filtered off and the filtrate shaken up in air to oxidise 9,10-dihydro-1,4-diaminophenazine to 1,4-diaminophenazine.

The solution was diluted and neutralised with ammonia solution, cooling during the neutralisation. The precipitated product was extracted with ether, the ether dried over anhydrous sodium sulphate and then evaporated on a steam bath. A purple amorphous residue was obtained which did not melt below 360° and could not be recrystallised.

The crude residue dissolved in alcohol to give a purple solution

which lost its colour with time and a sediment settled out.

Preparation of 1,4-diaminophenazine.

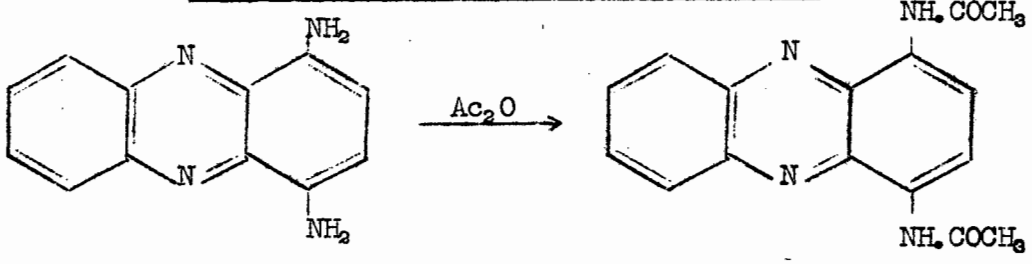


700 Mgm. of 1-amino-4-nitrophenazine were hydrogenated at 10 lbs. per sq. in. in 90 ml. of glacial acetic acid in the presence of 70 mgm. of Adam's catalyst until the solution was almost colourless.

The light red solution was filtered to remove the catalyst and then shaken in air for some time to oxidise the 9,10-dihydro-1,4-diaminophenazine to 1,4-diaminophenazine, the solution turning dark red on oxidation. This was diluted to 200 ml. and neutralised by the gradual addition of concentrated ammonia solution, keeping the temperature from rising above 25° by cooling in ice. The separated fine purplish precipitate was filtered off, washed and dried. 370 Mgm. of crude 1,4-diaminophenazine was obtained. On very rapid heating this compound melted with resolidification at 194° - 197°.

On attempting recrystallisations from some organic solvents the compound was decomposed. Freshly precipitated 1,4-diaminophenazine dissolves in concentrated hydrochloric acid solution to give a yellow-green solution turning yellow on dilution.

Preparation of 1,4-diacetamidophenazine.



300 Mgm. of finely crushed crude 1,4-diaminophenazine were treated with 10 ml. of acetic anhydride and left to stand at room temperature for 10 hours.

The reaction mixture was then poured into 120 ml. of cold water, the precipitated product filtered off, washed and dried. Approximately 400 mgm. of crude rust-red 1,4-diacetamidophenazine, softening at 255° and melting at 259° - 261°, were obtained. This crude compound was recrystallised from xylene and depending on the rate of cooling and the concentration either dark red compact needles or fine light red needles separated.

After three recrystallisations the melting point was constant at 261.5° - 263° and the yield had dropped to 140 mgm. (36%).

Analysis:		C	H	N
$C_{16}H_{14}N_4O_2$	requires	65.31%	4.80%	19.04%
	Found	65.00%	4.80%	19.23%.

1,4-Diacetamidophenazine has a reddish fluorescence. Dissolved in concentrated hydrochloric acid a wine coloured solution from which it precipitates on dilution was obtained. On boiling in dilute hydrochloric acid it rapidly dissolves to give a brownish solution.

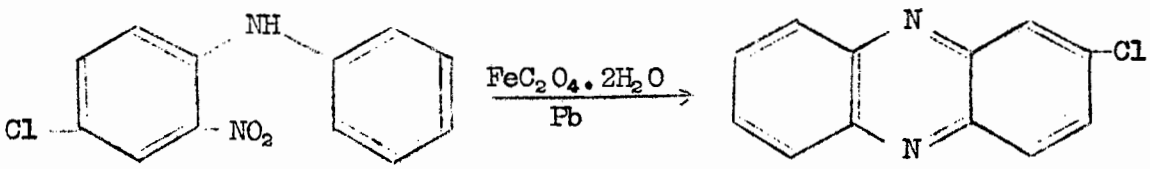
Attempted conversion of 1,4-diaminophenazine to 1,4-dihydroxyphenazine.

Refluxing 1,4-diaminophenazine with 3 N sulphuric acid for 17 hours, resulted in charred looking material which did not melt below 360° and could not be recrystallised.

SECTION IB.

Preparation of 2-chlorophenazine.

D.L. Vivian and J.L. Hartwell. J. Org. Chem. 18, 1068 (1953).



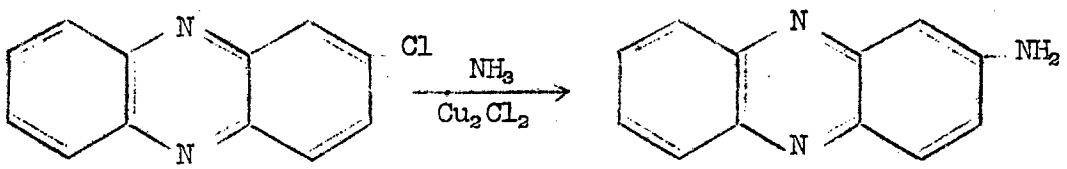
2-Chlorophenazine (m. pt. 135° - 136°) was obtained in 46% yield.

Attempted preparation of 2-aminophenazine.

0.5 Gms. of 2-chlorophenazine, 5 gms. of phenol, a little copper bronze and a little cuprous chloride were heated together at 170° - 180° in a slow stream of ammonia gas. The reaction mixture was cooled, made strongly acid by the addition of 6 N hydrochloric acid and exhaustively extracted with ether. The residual solution was neutralised, the precipitate filtered off, washed and dried. On heating this precipitate did not melt below 360°.

Preparation of 2-aminophenazine.

Compare I.J. Pachter and M.C. Kloetzel. J.A.C.S. 74, 971 (1952).



3 Gms. of 2-chlorophenazine, 0.6 gms. of cuprous chloride and a little copper bronze were heated in 100 ml. of almost saturated ammonia solution in a sealed tube at 190° - 200° for 24 hours. On cooling large dark red needles of 2-aminophenazine separated from the solution. The crystals were filtered off, washed and dried. 3 Gms. (theoretical yield) of crude 2-aminophenazine of melting point 260° - 275° were obtained.

Recrystallised from a 50% aqueous-alcoholic solution, in the presence of a little norite, 1.9 gms. of bright red needles of 2-aminophenazine of melting point 274° - 277° were obtained. On

repeated recrystallisation a melting point of 277° - 280° was attained.

Crystals of 2-aminophenazine have a slight dark red fluorescence. A xylene solution of 2-aminophenazine has a yellow-green fluorescence. Dissolved in concentrated hydrochloric acid a blue-green solution is obtained, turning red on dilution. The blue-green acid solution placed on filter paper appears as a deep red spot with deep red fluorescence. This spot turns orange, with a bright orange fluorescence in ammonia vapour.

The above authors obtained only a 13% yield of 2-aminophenazine of melting point 265° - 267°, under similar conditions, but in the absence of cuprous chloride.

In a shaking vessel the reaction went to completion in about 12 hours' time.

Attempted preparations of 2-acetamidophenazine.

(i) Compare J.B. Cohen and H.G. Crabtree J.C.S. 2055 (1921).

The crude product obtained by refluxing 2-aminophenazine with acetic anhydride and fused sodium acetate had a melting point of 145° - 180°. After three recrystallisations from methanol this product softened from about 140° and melted at 195° - 220°.

Analysis:	C	H
$C_{14}H_{11}N_3O$ requires	70.84%	4.67%
Found	67.23%	5.00%

(ii) Compare F. Kehrmann and E. Hoehn. Helv. chim. acta. 8, 223 (1925).

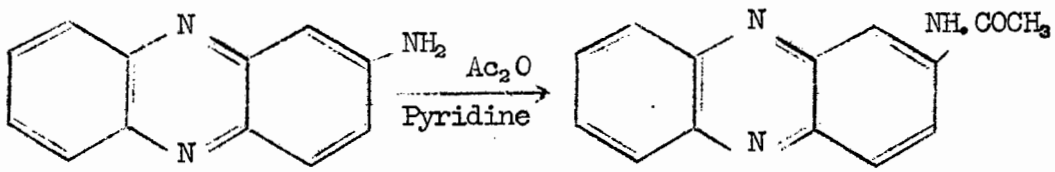
2-Aminophenazine, heated on a water-bath with acetic anhydride and anhydrous zinc chloride, gave a yellow product

which softened from 140° and melted at 190° with decomposition.

(iii) 2-Aminophenazine refluxed with pyridine and acetic anhydride gave a yellow product. This product was found to melt partly at 165° - 180°, but part of the product remained unmelted at 300°, when some decomposition was evident.

(iv) Acetylations of 2-aminophenazine with acetyl chloride and pyridine in the cold and then pouring the reaction mixture into cold water were not successful, as on standing the liberated hydrochloric acid hydrolysed the product.

Preparations of 2-acetamidophenazine.

(i) 

3 Gms. of 2-aminophenazine, 60 ml. of acetic anhydride and 30 ml. of pyridine were heated together on a steam bath for 45 minutes. After cooling the reaction mixture was poured into water, from which 2-acetamidophenazine separated as yellow needles after standing for some time. These were filtered off, washed, dried and found to soften at 150° and melt at 210°.

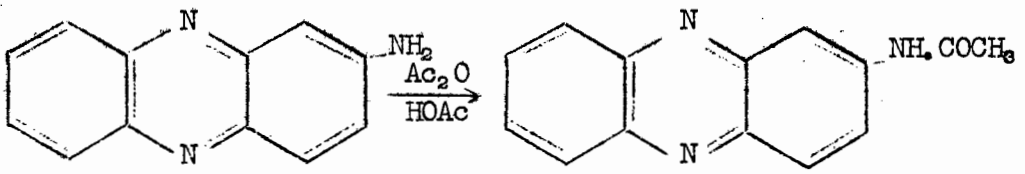
Recrystallised repeatedly from methanol the yellow needle like crystals of 2-acetamidophenazine were found to soften slightly from about 190° and melted at 231° - 234°.

Analysis:	C	H	N
$C_{14}H_{11}N_2O$ requires	70.84%	4.67%	17.70%
Found	66.29%	5.14%	16.57%
$C_{14}H_{11}N_3O.H_2O$ requires	65.86%	5.13%	16.46%.

The percentage loss in weight for $C_{14}H_{11}N_3O.H_2O$, on losing one molecule of water of crystallisation, was calculated to be 7.06%. A sample of this compound was heated at 100°, at about 20 mm., to constant weight and the loss in weight found to be 7.05%.

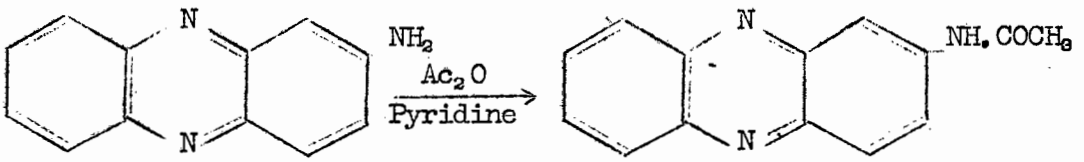
2-Acetamidophenazine has a yellow fluorescence. Dissolved in concentrated hydrochloric acid a red solution is obtained. Boiled with dilute hydrochloric acid 2-acetamidophenazine is hydrolysed to give a red solution.

(ii)



2-Acetamidophenazine was obtained by refluxing 350 mgm. of 2-aminophenazine with 10 ml. of acetic anhydride and 5 ml. of glacial acetic acid for 1 hour.

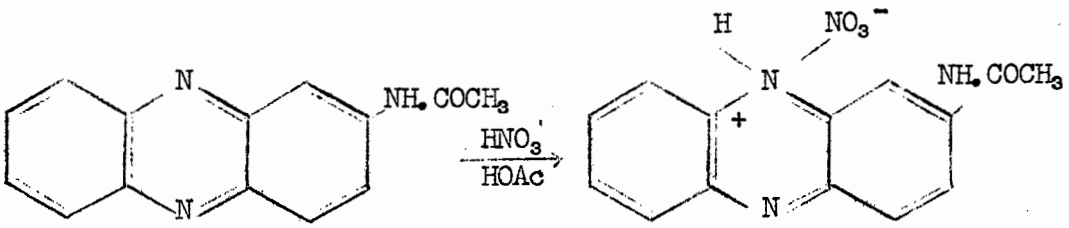
(iii)



2-Acetamidophenazine was successfully prepared by shaking 200 mgm. of 2-aminophenazine for 2 days at room temperature with 6 ml. of pyridine and 6 ml. of acetic anhydride.

Attempted nitration of 2-acetamidophenazine.

(i)



2.6 Gms. of 2-acetamidophenazine were dissolved in 13 ml. of glacial acetic acid and with vigorous stirring, maintaining the temperature below 30°, 2.6 ml. of nitric acid (S.G. 1.4) were slowly added. After about 0.3 ml. of nitric acid had been added a precipitate separated. The reaction mixture was allowed to stand at room temperature overnight, then slightly diluted, the orange precipitate filtered off, washed, dried and found to melt with decomposition at 165°.

This orange product was recrystallised from alcohol to give 1.6 gms. of a product melting with decomposition at 175°. For subsequent recrystallisations methanol was used. The melting point of the red needles remained constant at 175°, when decomposition took place.

Analysis:	C	H	N
Found	56.16%	4.14%	18.59%

This analysis was found to agree with that required by 2-acetamidophenazinium nitrate.

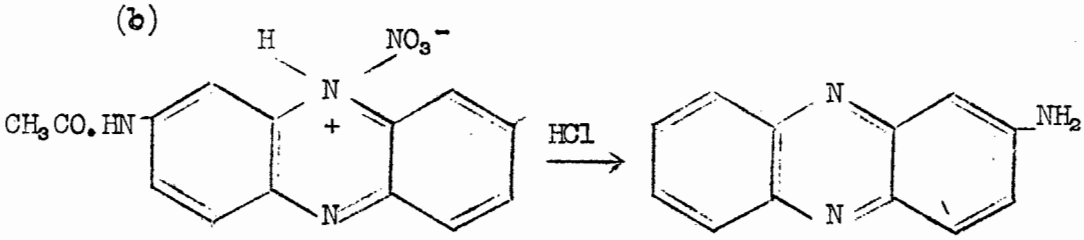
	C	H	N
$C_{14}H_{12}N_4O_4$ requires	55.91%	4.03%	18.66%.

2-Acetamidophenazinium nitrate has a slight dull red fluorescence and dissolves in water to give a red solution.

Conversion of 2-acetamidophenazinium nitrate to 2-acetamidophenazine and to 2-aminophenazine.

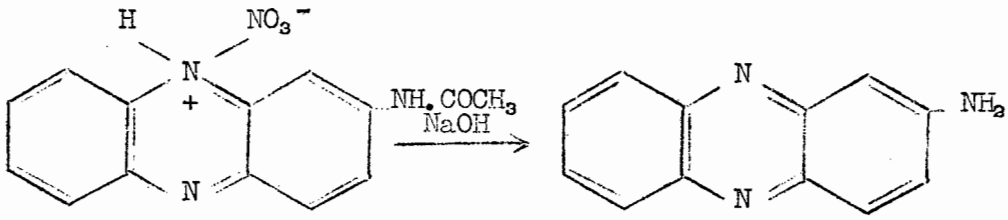
(a) 2-Acetamidophenazinium nitrate was dissolved in water and the red solution made just alkaline. The precipitated product was filtered off, washed, dried and recrystallised from methanol. On admixture with 2-acetamidophenazine no depression of the melting point was observed.

(b)



500 Mgm. of 2-acetamidophenazinium nitrate were refluxed with 10 ml. of 6 N hydrochloric acid for 30 minutes, cooled and made just alkaline. The precipitate was filtered off, washed, dried and recrystallised from a 50% aqueous-alcoholic solution. The red needles obtained, on admixture with 2-aminophenazine gave no depression of the melting point.

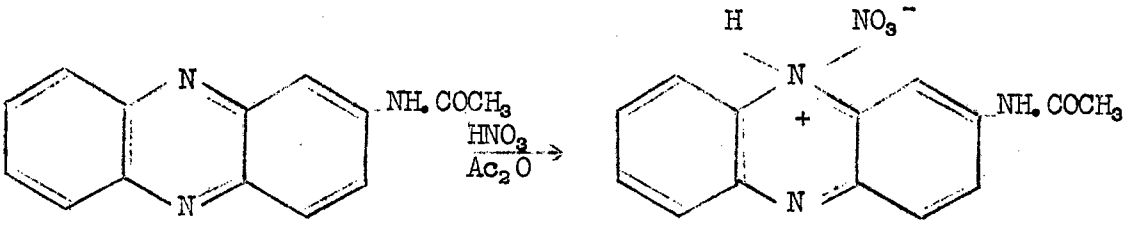
(c)



500 Mgm. of 2-acetamidophenazinium nitrate were refluxed for 1 hour with 20 ml. of 6 N sodium hydroxide. After cooling the red precipitate was filtered off and recrystallised from a 50% aqueous-alcoholic solution. The red needles gave

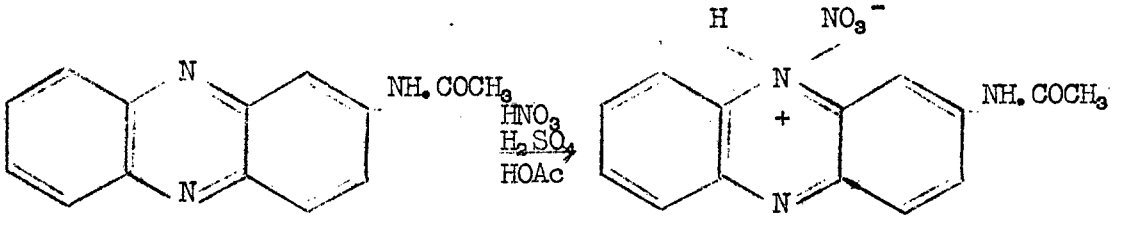
no depression of the melting point on admixture with 2-amino-phenazine.

(ii)



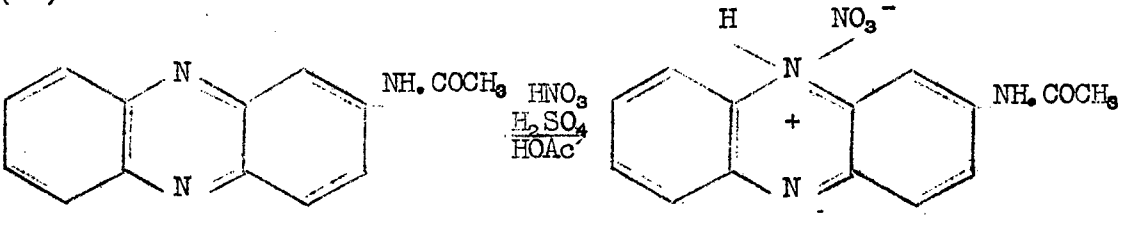
A poor yield of 2-acetamidophenazinium nitrate was obtained on adding, at 0°, a solution of 4.5 ml. of nitric acid (S.G. 1.5) in 12 ml. of acetic anhydride to a suspension of 700 mgm. of 2-acetamidophenazine in 10 ml. of acetic anhydride. On completion of the addition the reaction mixture was allowed to stand overnight at room temperature.

(iii)

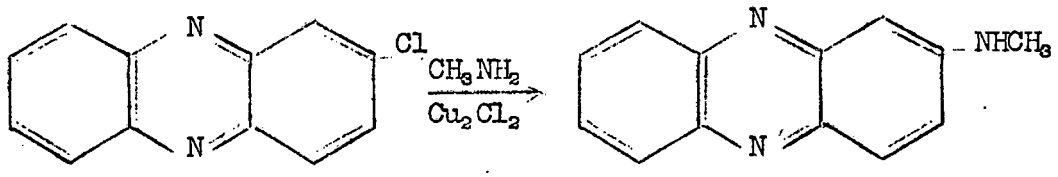


2 Ml. of fuming nitric acid (S.G. 1.5) was added to a solution of 2-acetamidophenazine in 5 ml. of glacial acetic acid and 3 ml. of concentrated sulphuric acid at 5° - 10°. After standing for 1 hour 2-acetamidophenazinium nitrate was isolated.

(iv)



Preparation of 2-methylaminophenazine.



1 Gm. of 2-chlorophenazine, 0.2 gms. of cuprous chloride and a little copper bronze were heated with 35 ml. of a 40% aqueous methylamine solution for 24 hours at approximately 160° - 170°. After cooling the reaction mixture was filtered and the tarry residue washed with a little water.

The greater part of the methylamine was removed from the combined filtrate and washings by evaporation at room temperature under reduced pressure. A good yield of crude 2-methylaminophenazine of melting point 165° - 173° separated.

This was recrystallised, in the presence of a little norite, by dissolving in a little boiling alcohol and adding water until the point of incipient precipitation was almost reached. After three recrystallisations the recovery was 200 mgm. of 2-methylaminophenazine of melting point 183° - 188°.

No satisfactory analysis was obtained for this compound.

Analysis:	C	H	N
$C_{13}H_{11}N_3$ requires	74.63%	5.30%	20.08%
Found	74.56%	6.08%	-
	72.64%	5.97%	18.61%
	73.11%	5.64%	17.80%.

2-Methylaminophenazine recrystallised either as jagged needles or fine red needles, depending on the rate of cooling and the ratio of alcohol to water. These crystals are brown-red in colour when

dry and dark red when moist. 2-Methylaminophenazine has an orange-red fluorescence and its alcoholic solution a bright orange-yellow fluorescence. Dissolved in concentrated hydrochloric acid a blue solution is obtained turning red on dilution. Recrystallisation from other solvents gave oils.

200° was found to be too high a reaction temperature, resulting in decomposition. Heating at 180° for 15 hours also gave the desired conversion.

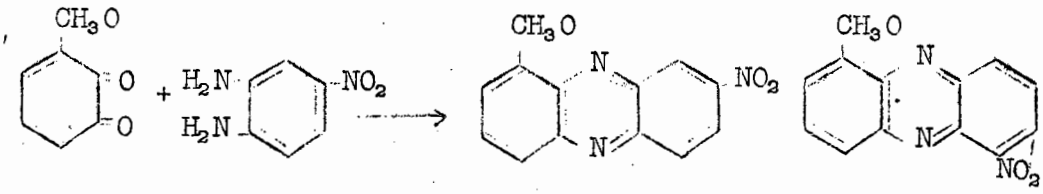
Attempted condensation of 2-chlorophenazine and Glycine.

No product could be isolated on heating 1 gm. of 2-chlorophenazine, 8 gms. of glycine, 0.2 gms. of cuprous chloride and a little copper bronze in 50 ml. of water at 180° for 12 hours.

SECTION II

Condensation of 4-nitro-o-phenylenediamine and 3-methoxy-o-quinone.

(i)



A solution of 5.5 gms. of 4-nitro-o-phenylenediamine in 1850 ml. of glacial acetic acid was added to a solution of 3-methoxy-o-quinone prepared by the method of Surrey[21] from 5 gms. of pyrogallol 1-monomethyl ether in 1250 ml. of dry benzene. After thorough shaking the solution was allowed to stand for about 20 hours.

The reaction mixture was filtered and the filtrate washed three or four times each, with water, with alkali and finally again with water. A large amount of sludge separated during the washings.

The washed benzene solution was dried over anhydrous sodium carbonate, then passed through an alumina column and eluted with dry benzene. A chromatogram consisting of a large yellowish band followed by a few smaller, darker, bands developed. Where the yellow band had been stopped for any period of time a dark band was found to be left on the alumina and this band could not be moved with benzene or chloroform as eluting solvent. Ether moved the band very slowly.

The yellow band came off the column as an orange-yellow solution and was collected in fractions of 300 - 400 ml. of

benzene and the benzene evaporated. The melting points of the residues on evaporation of the benzene from the various fractions were:

Fraction	Melting point	Comment
1	-	Too little to determine a m. pt.
2	-	" " " " " " "
3	182° - 200°	
4	183° - 210°	
5	225° - 240°	
6	(190°)220° - 234°	First signs of melting at 190°
7	(179°)210° - 230°	" " " " " 179°
8	160° - 187°	
9	-	
10	-	

After the yellow band had been eluted from the column the dark bands where the yellow zone had been stopped were eluted with water. They came off the column as a reddish solution. No colour change was observed on adding alkali to this solution. On adding hydrochloric acid to this solution a precipitate was obtained which did not dissolve on adding an excess of concentrated hydrochloric acid, but could be redissolved on adding alkali. Insufficient of this precipitate was obtained to do a melting point.

Each of the fractions obtained from the yellow zone were individually recrystallised from acetone and their melting points found to shift towards the same value. The fractions were combined and recrystallised from acetone to give a melting point 255° - 258°. On extremely critical observation it was thought that there were very slight signs of melting at about 235°. The recovery was very small.

Analysis:		C	H	N
$C_{13}H_9N_3O_3$	requires	61.17%	3.56%	16.46%
	Found	61.26%	3.72%	16.35%

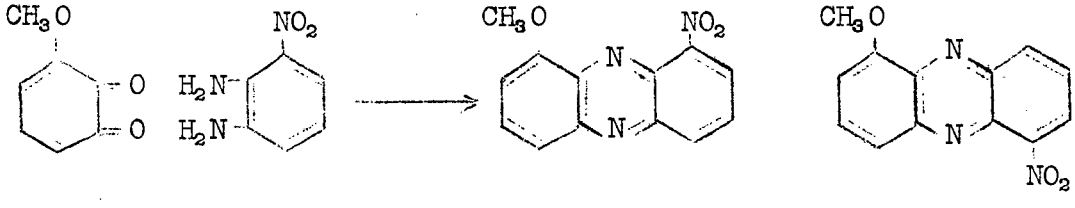
The compound isolated must be 1-methoxy-6-nitrophenazine or (and)

1-methoxy-7-nitrophenazine.

These orange needles had an orange fluorescence. Dissolved in concentrated hydrochloric acid a purple solution is obtained from which it is precipitated on dilution.

A successful hydrogenation, either in glacial acetic acid or in absolute alcohol, could not be carried out on the small amount of this condensate eventually isolated, with palladium-charcoal as catalyst.

Condensation of 3-methoxy-o-quinone and 3-nitro-o-phenylenediamine.



A solution of 3-methoxy-o-quinone in 1250 ml. of dry benzene prepared by the method of Surrey[21] from 5.7 gms. of pyrogallol 1-monomethyl ether was added slowly, with vigorous swirling, to a solution of 6 gms. of 3-nitro-o-phenylenediamine in 1000 ml. of glacial acetic acid and 1500 ml. of dry benzene and left to stand for 5 hours.

The solution was then divided into two portions and each portion washed repeatedly first with water, then with 5% sodium hydroxide solution and finally again with water. These washed benzene solutions were combined and shaken for 15 hours with 110 gms. of anhydrous sodium carbonate and 10 gms. of norite and after filtration passed through an alumina column and eluted with dry benzene. The chromatogram which developed consisted of a large frontal orange-yellow band followed

by some very much smaller bands.

The yellow zone was eluted, the eluate collected in fractions of 300 - 400 ml. and the benzene then evaporated. All the fractions had melting points in the vicinity of 200° and recrystallised individually the melting points of the various fractions attained the same value.

All the fractions were combined to give 1.2 gms. of crude product. This was recrystallised repeatedly from alcohol to give orange needles showing slight signs of melting from 200° and melting sharply at 205° - 206°.

Analysis:		C	H	N
$C_{13}H_9N_3O_3$	requires	61.17%	3.56%	16.46%
	Found	62.0%	3.73%	16.1%

The compound isolated here is 1-methoxy-5-nitrophenazine or (and) 1-methoxy-8-nitrophenazine.

This product has an orange fluorescence. Dissolved in concentrated hydrochloric acid a purple solution is obtained from which it is precipitated on dilution.

Preparation of 1-methoxy-5(or 8)-aminophenazine.

350 Mgm. of 1-methoxy-5(or 8)-nitrophenazine were hydrogenated in 35 ml. of glacial acetic acid in the presence of Adam's catalyst at 10 lbs. per sq. in. for 3 hours.

The wine coloured solution was filtered to remove the catalyst and the filtrate shaken in the air to oxidise the 9,10-dihydro-1-methoxy-5(or 8)-aminophenazine to 1-methoxy-5(or 8)-aminophenazine the solution turning dark red. After slight dilution the solution was neutralised by the gradual addition of ammonia solution, maintaining the temperature below 30°. The precipitated product was filtered

off, washed, dried and found to have a melting point of 176° - 180°.

Recrystallised from petroleum ether (b. pt. 80° - 100° or b. pt. 120° - 180°) dark red needles were obtained. For analysis 1-methoxy -5(or 8)-aminophenazine was recrystallised to a melting point of 194° - 197°.

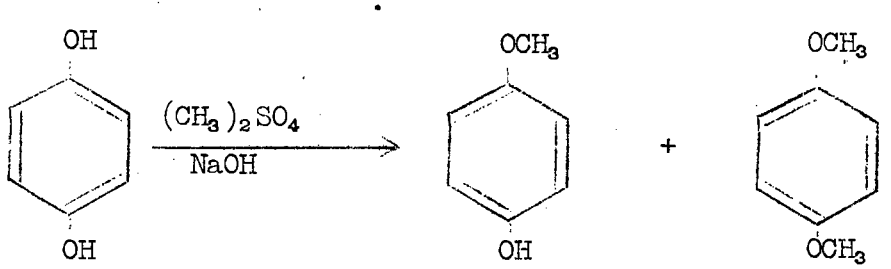
Analysis:	C	H	N
$C_{13}H_{11}N_3O$ requires	69.31%	4.92%	18.65%
Found	70.03%	4.67%	18.50%.

These crystals dissolve in concentrated hydrochloric acid to give a reddish solution turning blue on dilution. A petroleum ether solution of 1-methoxy-5(or 8)-aminophenazine showed a bright orange-yellow fluorescence but the crystals only a faint dark red fluorescence.

Paper chromatograms of both 1-methoxy-5(or 8)-nitrophenazine and 1-methoxy-5(or 8)-aminophenazine were done to determine whether a mixture of isomers was present or not. No conclusive evidence was obtained either way as the spots moved too close to the solvent front with all the solvents used.

Preparation of quinol-monomethyl ether.

R. Robinson and J.C. Smith, J.C.S. 393 (1926).



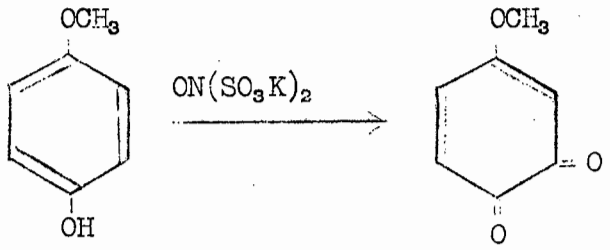
A 23% yield of quinol-monomethyl ether, of melting point 53° - 57°, was obtained.

Preparation of potassium nitrosodisulphonate.

From a private communication from H.J. Teuber of the procedure of F. Raschig. Chem. Zentr. 95, 448 (1924).

Preparation of 4-methoxy-o-quinone.

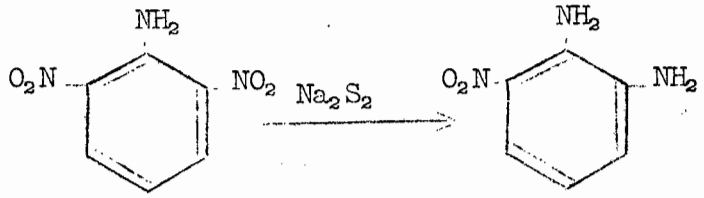
H.J. Teuber and G. Staiger. Ber. 88, 825 (1955).



A theoretical yield of 4-methoxy-o-quinone was obtained.

Preparation of 3-nitro-o-phenylenediamine.

Compare J.L. Rabinowitz and E.C. Wagner. J.A.C.S., 73, 3034 (1951).



This reduction is recorded as it was done in aqueous solution. The above authors did the reduction in an aqueous-alcoholic solution.

6.5 Gms. of flowers of sulphur and 26.0 gms. of sodium sulphide crystals ($Na_2S.9H_2O$) were boiled in 100 ml. of water until a clear solution resulted. This solution was then added gradually from a dropping funnel, over a period of 20 minutes, to a gently boiling suspension of 18.3 gms. of 2,6-dinitroaniline in 750 ml. of water

with vigorous stirring. On completion of the addition the reaction solution was boiled for a further 20 minutes and then filtered hot. The filtrate was cooled in ice for a few hours and the separated 3-nitro-o-phenylenediamine filtered off and dried.

13 - 14 Gms. of 3-nitro-o-phenylenediamine of melting point 154° - 158° were obtained. Recrystallised from alcohol in the presence of norite 9 - 10 gms. (65%) of red needles of melting point 156° - 158° were obtained.

Attempted condensation of 4-methoxy-o-quinone and 3-nitro-o-phenylenediamine.

(i) A solution of 3.1 gms. of 3-nitro-o-phenylenediamine in 400 ml. of glacial acetic acid and 100 ml. of dry benzene was treated with a solution of 2.8 gms. of 4-methoxy-o-quinone in 600 ml. of dry benzene, with vigorous stirring, and left to stand for 6 hours. A further 200 ml. of benzene were then added and the reaction mixture washed repeatedly, first with water, then with a 5% sodium hydroxide solution and finally again with water.

The washed benzene solution was shaken up for a day with 50 gms. of anhydrous sodium carbonate and 5 gms. of norite, filtered and the filtrate passed through an alumina column. A faint yellow zone developed. This darkened with time, leaving a dark band which could only be moved with difficulty.

The eluate was slightly coloured and on removal of the solvent a very small amount of yellowish material of indefinite melting point remained. This could not be recrystallised.

(ii) A solution of 3.3 gms. of 3-nitro-o-phenylenediamine in 1000 ml. of glacial acetic acid was added to a solution of 3 gms. of 4-methoxy-o-quinone in 1450 ml. of dry benzene. The reaction mixture was left to stand overnight.

The solution was then repeatedly washed, first with water, then 2 N sodium hydroxide solution and finally again with water. The benzene solution was then shaken for a day with 50 gms. of anhydrous sodium carbonate and 3 gms. of norite, filtered and the filtrate shaken up with 10 gms. of alumina. After removal of the alumina by filtration, the benzene was evaporated under reduced pressure at about 60°.

A very small amount of dark material of melting point 140° - 190° remained. This could not be recrystallised to improve the melting point.

Attempted condensation of 4-methoxy-o-quinone and 4-nitro-o--phenylenediamine.

(i) 2.7 Gms. of 4-methoxy-o-quinone were dissolved in 70 ml. of glacial acetic acid and while stirring vigorously 3.1 gms. of 4-nitro-o-phenylenediamine were added in very small portions. After standing for 16 hours the reaction mixture was filtered and the residual black material well washed and dried.

The black residue appeared to melt from about 220°. It was vacuum sublimed to give an extremely small amount of orange sublimate of melting point 140° - 155°, which dissolved in concentrated hydrochloric acid to give a yellowish green solution. There was insufficient of this material for recrystallisation or analysis.

The filtrate and washings from above were combined and more water added until no more precipitate separated. This precipitate was filtered off, washed, dried and vacuum sublimed. A yellowish sublimate of melting point 194° - 200°, was preceded by an extremely small amount of dirty yellow sublimate of melting point 152° - 160°. The sublimate was recrystallised from butanol to give reddish crystals of melting point 206° - 214°.

The yield was too small for analysis. Dissolved in concentrated hydrochloric acid a deep red solution was obtained from which the product was precipitated on dilution.

(ii) To a solution of 3 gms. of 4-methoxy-o-quinone in 1750 ml. of dry benzene, was added a solution of 3.3 gms. of 4-nitro-o -phenylenediamine in 1500 ml. of glacial acetic acid and 250 ml. of dry benzene, with vigorous swirling and allowed to stand for 3 hours. The reaction solution was then washed repeatedly, first with water, then with 2 N sodium hydroxide solution and finally again with water.

The benzene solution was dried over anhydrous sodium carbonate, passed through an alumina column and eluted with dry benzene. A relatively large yellow-green zone was followed by a dark and a reddish band. The bands moved very slowly and the yellow zone darkened on the alumina with time, and this dark band could not be moved, even by passing water through the column.

(iii) The previous condensation was repeated and the washed benzene solution shaken with 50 gms. of anhydrous sodium carbonate and 1 gm. of norite for 24 hours, filtered and the filtrate shaken up with 20 gms. of alumina. After removal of the alumina by filtration the benzene was evaporated under reduced pressure at 60°.

A dirty yellow residue remained, which, on heating showed a melting range of 160° - 200°, finally decomposing. The yield was extremely small. Recrystallised from alcohol the melting point could be raised to 204° - 215°.

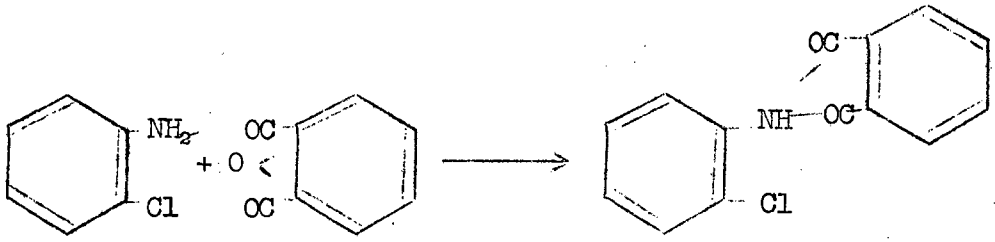
This material had an amorphous appearance, a bright yellow fluorescence and dissolved in concentrated hydrochloric acid to give a reddish solution from which it was precipitated on dilution. There was insufficient material for analysis.

SECTION IIIA

Preparation of 2-chloro-5-nitroaniline.

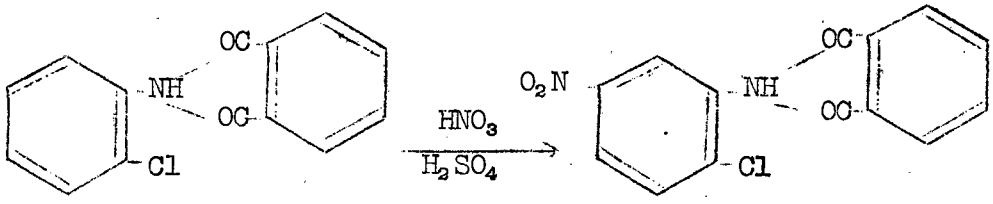
C. Buchanan and S.H. Graham. J.C.S. 3435 (1949).

(i) Preparation of N-(o-chlorophenyl)-phthalimide.



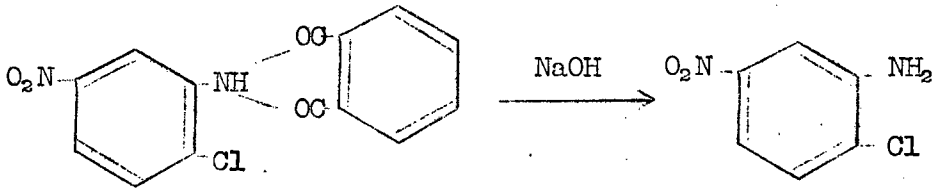
A 70% yield of N-(o-chlorophenyl)-phthalimide of melting point 139° - 141° was obtained.

(ii) Preparation of N-(2-chloro-5-nitrophenyl)-phthalimide



A 71% yield of N-(2-chloro-5-nitrophenyl)-phthalimide of melting point 196° - 197° was obtained.

(iii) Preparation of 2-chloro-5-nitroaniline.



2-Chloro-5-nitroaniline of melting point 138° - 140° was obtained in 98% yield.

Attempted preparations of 2,6-dinitrophenazine.

(i) No condensation took place on refluxing 4 gms. of 2-chloro -5-nitroaniline, 4.5 gms. of freshly calcined potassium carbonate and 0.2 gms. of copper bronze in 10 ml. of nitrobenzene for 30 minutes.

(ii) No condensation took place on refluxing for 30 minutes in 20 ml. of nitrobenzene, 15 gms. of 2-chloro-5-nitroaniline, 8 gms. of fused sodium acetate and 0.1 gm. of copper bronze.

(iii) Only tarry and charred material was obtained on refluxing for 9 hours, in 10 ml. of nitrobenzene, 2.5 gms. of 2-chloro -5-nitroaniline, 2.5 gms. of calcined potassium carbonate and 0.4 gm. of copper bronze.

(iv) Only charred material was obtained by refluxing 2.5 gms. of 2-chloro-5-nitroaniline, 2.5 gms. of fused sodium acetate and 0.4 gms. of copper bronze for 9 hours in 10 ml. nitrobenzene.

(v) No condensation took place on heating together, 4 gms. of 2-chloro-5-nitroaniline, 4.5 gms. of calcined potassium carbonate and 0.3 gms. of copper bronze at 180° - 210° for one hour.

(vi) No condensation took place on heating together 4 gms. of 2-chloro-5-nitroaniline, 5 gms. of fused sodium acetate and a little copper bronze.

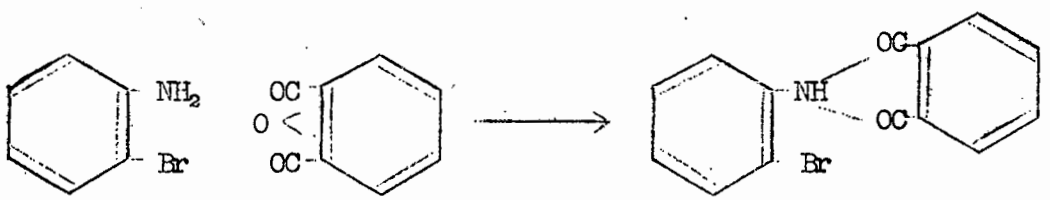
(vii) A violent explosion resulted on heating together 2.7 gms. of 2-chloro-5-nitroaniline, 3.5 gms. of calcined potassium carbonate and 0.5 gm. of copper bronze in a sealed tube at 400°.

Heating at 240° also resulted in an explosion.

(viii) On heating 3 gms. of 2-chloro-5-nitroaniline and 4 gms. of fused sodium acetate together in a sealed tube at 300° a violent explosion resulted.

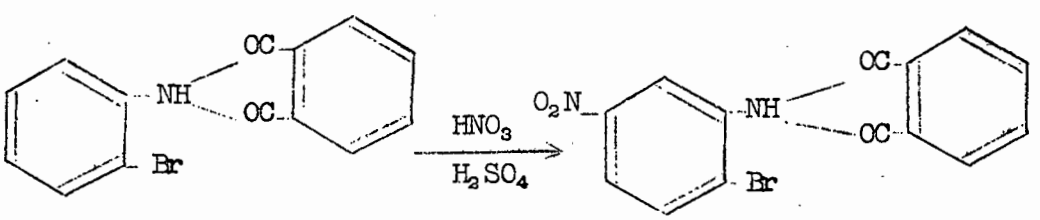
Preparation of 2-bromo-5-nitroaniline.

(i) Preparation of N-(o-bromophenyl)-phthalimide.



25 Gms. of o-bromoaniline and 21.5 gms. of phthalic anhydride were heated together at 120° for 20 minutes and then for 40 minutes at 180°. On cooling the melt solidified to a white mass which was recrystallised from alcohol to give 31 gms. (67%) of N-(o-bromophenyl)-phthalimide of melting point 130° - 132°.

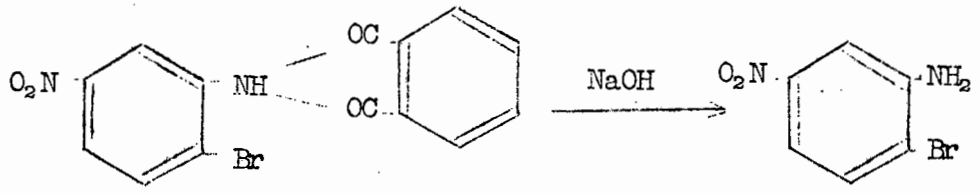
(ii) Preparation of N-(2-bromo-5-nitrophenyl)-phthalimide.



Maintaining the temperature at 30° - 40°, 23 ml. of nitric acid (S.G. 1.4) was added, with stirring, to 30 gms. of N-(o-bromophenyl)-phthalimide partly dissolved in 100 ml. of concentrated sulphuric acid. After standing for one hour, the reaction mixture was poured into 600 ml. of water and the precipitate filtered off, washed, dried and recrystallised

from glacial acetic acid. 25 Gms. (72%) of N-(2-bromo-5 -nitrophenyl)-phthalimide of m. pt. 232° - 234° was obtained.

(iii) Preparation of 2-bromo-5-nitroaniline.



25 Gms. of N-(2-bromo-5-nitrophenyl)-phthalimide were boiled in 210 ml. of 2 N sodium hydroxide for 2 hours. The product was filtered from the cooled reaction mixture, washed, dried and recrystallised from alcohol to give 14 gms. (90%) of 2-bromo-5-nitroaniline of melting point 140° - 141°.

Attempted preparations of 2,6-dinitrophenazine.

(i) No condensation took place on refluxing 2.5 gms. of 2-bromo -5-nitroaniline, 2.5 gms. of fused sodium acetate and 0.1 gms. of copper bronze in 10 ml. of nitrobenzene for 30 minutes.

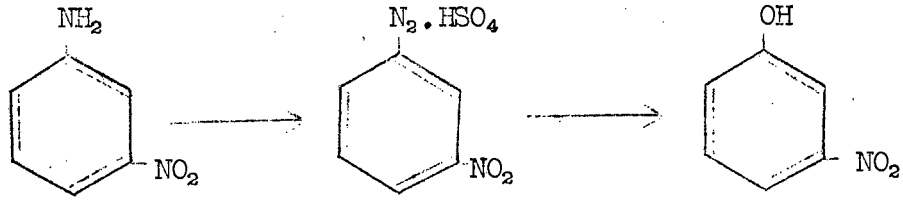
(ii) No pure product could be isolated on refluxing 3 gms. of 2-bromo-5-nitroaniline, 4 gms. of anhydrous sodium carbonate and 0.4 gms. of copper bronze in 10 ml. of nitrobenzene for 1 hour.

(iii) No pure product could be isolated on refluxing for 9 hours, 2.5 gms. of 2-bromo-5-nitroaniline, 2.5 gms. of calcined potassium carbonate and 0.4 gms. of copper bronze in 10 ml. of nitrobenzene.

(iv) No condensation took place on refluxing for 30 minutes 5 gms. of 2-bromo-5-nitroaniline, 3 gms. of calcined potassium carbonate and 0.5 gms. of potassium iodide in 15 ml. of dry nitrobenzene.

Preparation of m-nitrophenol.

Vogel. Practical Organic Chemistry, 588.



A 63% yield of m-nitrophenol was obtained by distilling the crude compound isolated and collecting the fraction at 169° - 171° at 17 mm. The melting point of this product was 96° - 98°.

Attempted preparation of 2-iodo-3-nitrophenol.

Compare R.L. Datta and N. Prosad. J.A.C.S. 39, 441 (1917).

50 Gms. of m-nitrophenol were dissolved in 600 ml. of 30% ammonia solution, at 50° - 60°, and treated very slowly with about 230 ml. of an iodine solution (100 gms. of iodine and 160 gms. of potassium iodide dissolved in 250 ml. of water) and left to stand overnight. 140 Gms. of the ammonium salt of 2-iodo-3-nitrophenol were filtered off and recrystallised from glacial acetic acid to give 53 gms. of "2-iodo-3-nitrophenol" of melting point 130° - 136°. Recrystallised again the melting point rose to 138° - 142°.

The authors quote their product as being 2-iodo-3-nitrophenol, with a melting point of 134°. As the melting point of 6-iodo-m-nitrophenol is given [86] as 146° - 147° and the melting point of the product obtained was 138° - 142° it would appear that 6-iodo-m-nitrophenol is possibly a product of this reaction.

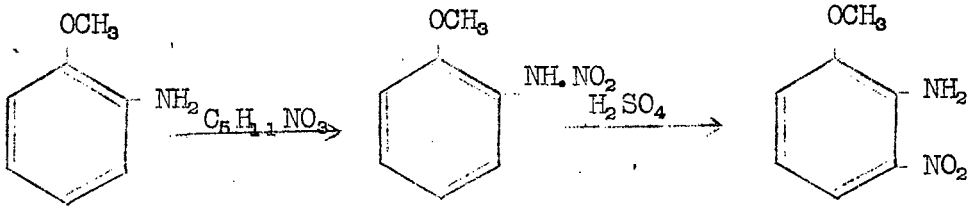
Considerations of steric hindrance make the formation of 6-iodo-m-nitrophenol more probable than that of 2-iodo-3-nitrophenol

on iodination of m-nitrophenol.

Due to the dubious nature of the product this preparation was discarded.

Preparation of 3-nitro-o-anisidine.

Compare E.S. Lane and C. Williams, J.C.S. 2977 (1954).



As the authors did not describe this synthesis in detail, the procedure followed was recorded.

In a dry nitrogen atmosphere, 45 gms. of clean dry potassium were dissolved in 190 ml. of "super dry" alcohol, with stirring and heating. After all the potassium had dissolved, the solution was cooled to about 30°, 184 ml. of dry ether added with stirring, then cooled to -10° and 151 ml. of amylnitrate added. Stirring was continued for 15 minutes after the last addition and then 123 ml. of o-anisidine were added in one portion, with vigorous stirring.

The reaction mixture was kept at -10° for a further 30 minutes and then allowed to stand at room temperature for two hours, stirring all the time. The yellowish potassium salt of o-methoxy-phenyl-nitramine, which started separating soon after the addition of the o-anisidine, was then filtered off, washed with dry ether and sucked dry. 100 Gms. of this salt were obtained.

The potassium salt of o-methoxy-phenylnitramine was added in small portions, over a long period, with vigorous stirring, to 160 ml. of concentrated sulphuric acid and 106 ml. of water at -30°. On

completion of the addition the temperature was maintained at -30° to -25° for a further 3 hours and then allowed to rise to room temperature overnight. The reaction mixture was then poured into 2 litres of water and neutralised with concentrated ammonia solution.

The precipitated product was filtered off, washed, dried and vacuum distilled. 56 Gms. (30%) of crude 3-nitro-o-anisidine, of melting point 65° - 71°, were collected between 126° and 134° at 0.33 mm. Recrystallised from methanol 30 gms. of 3-nitro-o -anisidine of melting point 72° - 75° were recovered.

Attempted preparation of 2,6-dinitrochlorobenzene.

Compare W. Borsche and D. Rantscheff. Ann. 379, 152.

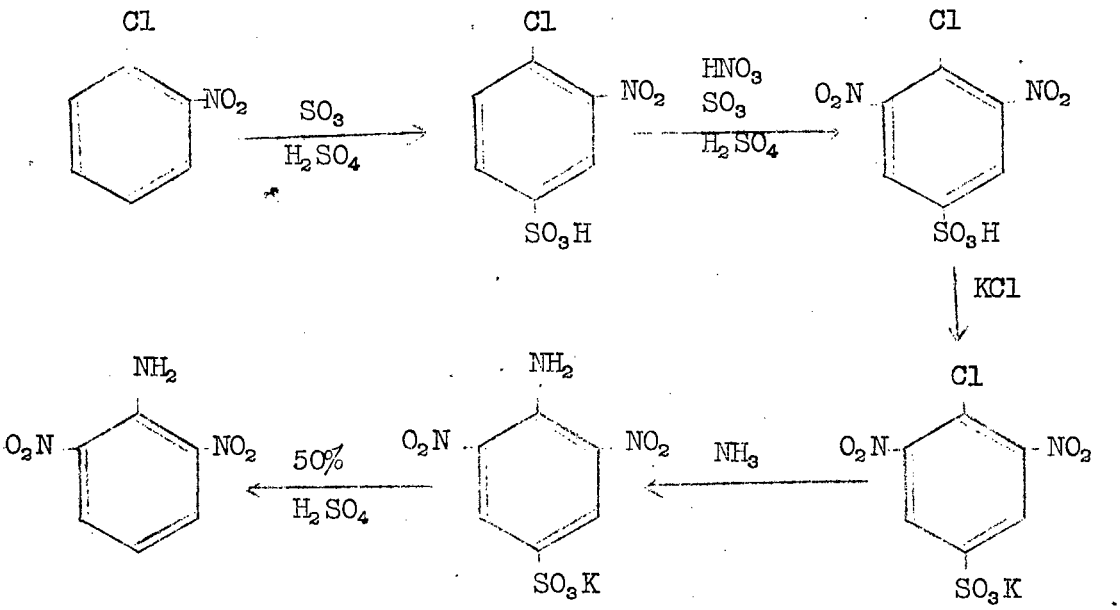
The resulting mixture of 2,6-dinitrochlorobenzene and 2,4-dinitrochlorobenzene, obtained by nitration of o-chloronitrobenzene, could not be successfully separated as described by the above authors.

Attempted separation of the isomers on alumina, using petroleum ether as eluant, was not successful either.

Preparation of 2,6-dinitroaniline.

J.L. Rabinowitz and E.C. Wagner. J.A.C.S. 73, 3034 (1951)

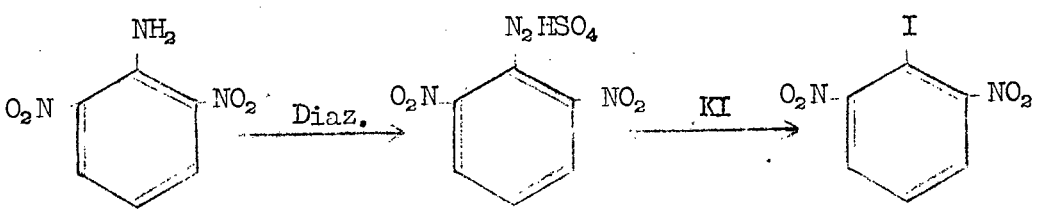
and H.P. Schultz. Org. Syn. 31, 45.



A 43% yield, based on o-chloronitrobenzene, of 2,6-dinitroaniline of melting point 136° - 139°, was obtained by preparing the potassium salt of 4-amino-3,5-dinitrobenzene sulphonic acid by the method of Rabinowitz and Wagner and effecting the desulphonation by the method of Schultz.

Preparation of 2,6-dinitro-iodobenzene.

Compare Korner and Contardi. R.A.L. [5] 23 II, 570.



10 Gms. of 2,6-dinitroaniline were introduced into a solution of 75 ml. of concentrated sulphuric acid and 40 ml. of water. 20 Gms. of crushed ice were added and then stirred to a homogeneous sludge. Maintaining the temperature at 0° - 5°, by cooling in ice, and with vigorous stirring, a solution of 3.8 gms. of sodium nitrite

in 40 ml. of water was slowly added. On completion of the addition, the reaction mixture was vigorously stirred for a further period of at least 1 hour, keeping the temperature at 0° - 5°.

A little urea was then added to destroy any excess nitrous acid and a little cold water to dilute the diazonium solution. The solution was then added slowly, from a dropping funnel, after filtering off any unchanged 2,6-dinitroaniline with glass wool, to a solution of 35 gms. of potassium iodide in 70 ml. of water at room temperature, stirring vigorously. On completion of the addition, the reaction mixture was heated on a water-bath for 30 minutes to complete the reaction.

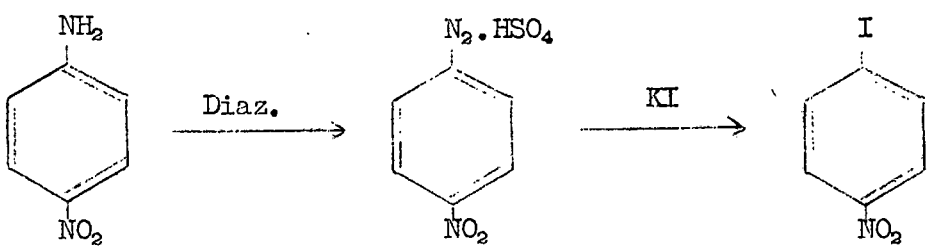
The reaction mixture was cooled, filtered and the precipitate washed and dried. The theoretical yield of crude 2,6-dinitro-iodobenzene of melting point 108° - 113° was obtained. Recrystallised from alcohol the recovery was 12.5 gms. (77%) of 2,6-dinitro-iodo-benzene (m. pt. 111° - 113°).

This could be recrystallised to a melting point of 114° - 116°.

Only charred material was recovered after attempting the diazotisation of 2,6-dinitroaniline with nitrosyl sulphuric acid.

Preparation of p-iodo-nitrobenzene.

Compare A. Daeyer. Ber. 38, 2760 (1905).

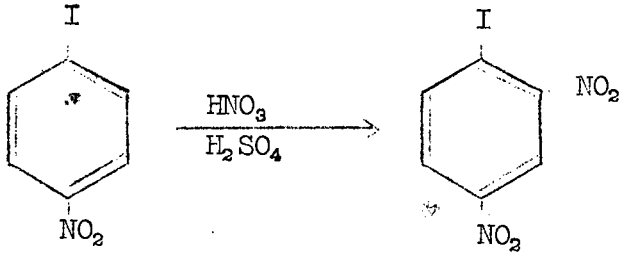


A 95% yield of p-iodonitrobenzene (m. pt. 170° - 173°) was

obtained.

Preparation of 2,4-dinitro-iodobenzene.

Compare Korner. Jahresberichte 322, (1875).



p-Iodonitrobenzene instead of o-iodonitrobenzene was nitrated.

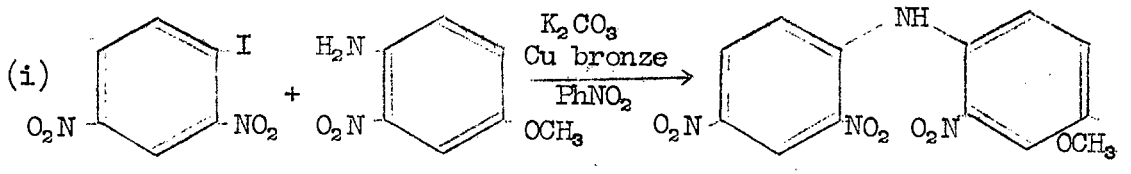
A 76% yield of 2,4-dinitroiodobenzene (m. pt. 84° - 87°) was obtained.

Attempted preparation of 2,4,2'-trinitro-4'-methoxydiphenylamine.

(i) 4.2 Gms. of 4-methoxy-2-nitroaniline and 5.05 gms. of 2,4-dinitro-chlorobenzene were refluxed in 60 ml. of 96% alcohol in the presence of 6 gms. of sodium acetate crystals for 6 hours. Only unchanged starting material could be isolated from the reaction mixture.

(ii) Without a solvent for the reagents the condensation was not successful.

Preparation of 2,4,2'-trinitro-4'-methoxydiphenylamine.



A mixture of 8.82 gms. of 2,4-dinitro-iodobenzene, 5.04 gms. of 4-methoxy-2-nitroaniline, 6 gms. of calcined potassium carbonate and 0.3 gms. of copper bronze was heated together, with occasional vigorous shaking, in 20 ml. of nitrobenzene at 140° for 10 hours.

The reaction mixture was then thoroughly shaken up with 175 ml. of absolute alcohol, chilled in ice and filtered. The residue was acidified with 60 ml. of 3 N hydrochloric acid solution, well shaken up, filtered and the residue well washed with water.

4.9 Gms. of a dark product of melting point 154° - 160° was obtained. Recrystallised from alcohol in the presence of a little norite, 3.2 gms. (32%) of 2,4,2'-trinitro-4'-methoxydiphenylamine of melting point 161° - 165° were obtained as fine orange needles. Further recrystallisations raised the melting point to 163° - 167°.

Analysis		C	H	N
$C_{13}H_{10}N_4O_7$	requires	46.71%	3.02%	16.77%
	Found	47.1%	2.73%	16.83%

Heating the reagents for only 3 hours gave a yield of about 10% of crude 2,4,2'-trinitro-4'-methoxydiphenylamine. It was found that the yield dropped slightly with increasing quantities of starting material. Removal of the nitrobenzene with alcohol was preferred to steam distillation of the reaction mixture, as being much quicker and giving a purer product in only slightly smaller yield.

(ii) 4.2 Gms. of 4-methoxy-2-nitroaniline, 5.05 gms. of 2,4-dinitro-chlorobenzene, 0.2 gms. of copper bronze and 3.0 gms. of calcined potassium carbonate were heated at 210° for 15 minutes in 10 ml. of nitrobenzene, shaking vigorously throughout.

The cooled reaction mixture was vigorously shaken with 50 ml. of alcohol, chilled and filtered. The residue was shaken up with 30 ml. of 3 N hydrochloric acid, filtered and the residue well washed with water. Recrystallised from alcohol in the presence of a little norite, 1.4 gms. (17%) of 2,4,2'-trinitro-4'-methoxydiphenylamine of melting point 158° - 162° were obtained.

(iii) The above procedure using 2,4-dinitro-iodobenzene instead of the chloro compound gave only a 10% yield.

Attempted sodium and methanol ring closure of 2,4,2'-trinitro -4'-methoxydiphenylamine.

41.4 Gms. of clean, dry sodium were added to a suspension of 3.34 gms. of 2,4,2'-trinitro-4'-methoxydiphenylamine in 160 ml. of absolute methanol, under anhydrous conditions, at such a rate that the mixture refluxed gently. A further 20 ml. of absolute methanol was then added to dissolve unreacted sodium.

The reaction mixture was then heated on a water-bath for 30 minutes, allowed to stand for 1½ hours, then heated for a further 2 hours and finally the greater part of the methanol was distilled off. After removal of the methanol the reaction mixture was poured into slightly more than its own volume of cold water. A dark precipitate was obtained, filtered off, washed and dried. On heating, this product did not melt below 360°. It could not be recrystallised and on vacuum sublimation at 240° and 0.3 mm. an extremely small amount of yellow sublimate was obtained. There was not sufficient for analysis and it could not be recrystallised,

Attempted reduction and ring closure of 2,4,2'-trinitro-4'-methoxydiphenylamine to give a phenazine.

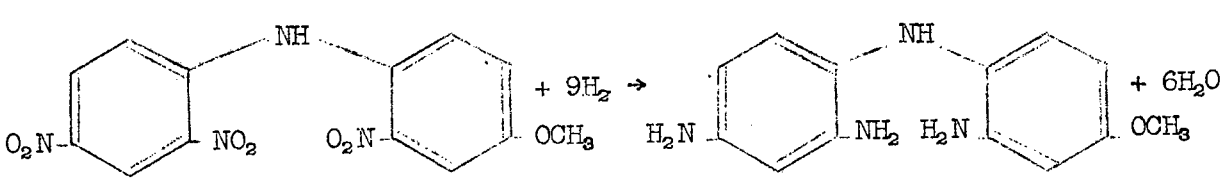
11 Gms. of A.R. tin were dissolved in concentrated hydrochloric acid and while gently boiling, 3.34 gms. of 2,4,2'-trinitro-4'-methoxydiphenylamine were added in small fractions to this solution. When the addition had been completed the reaction mixture was boiled for 30 minutes and then heated on a water-bath for 2 hours. A clear reddish solution resulted, was left to stand overnight, then heated in a sealed tube at 110° - 130° for 3½ hours and left to stand at room temperature for 3 days.

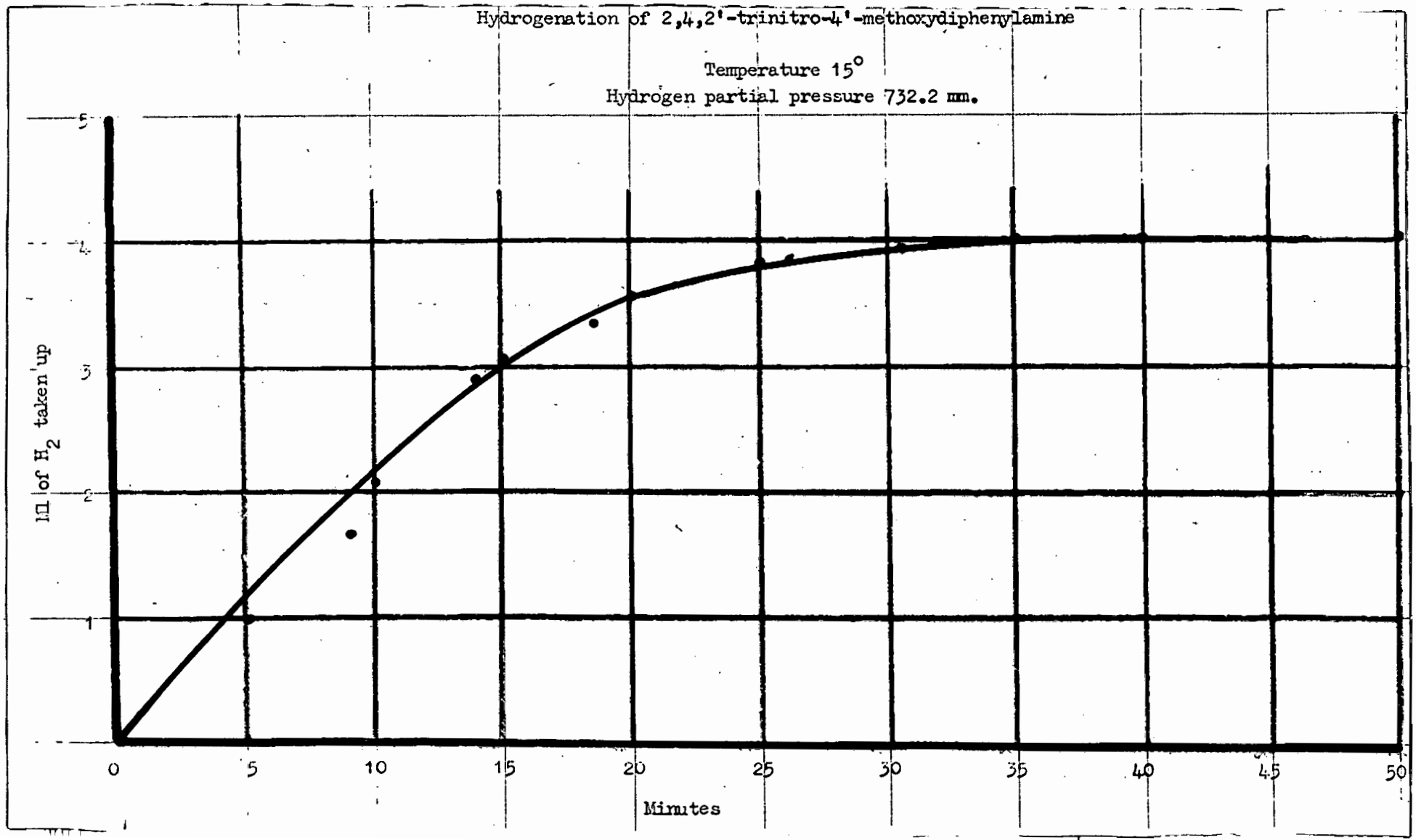
A blue green solution, containing light green crystals, was obtained. This was brought to a pH of about 13 and exhaustively extracted with ether. On evaporation of the ether extract a small amount of oily residue was obtained. This could not be solidified or purified.

The alkaline residue was adjusted to a pH of 7, saturated with hydrogen sulphide, all the tin removed as the sulphide by filtration and the filtrate extracted with ether. A reddish ethereal extract was obtained which on evaporation deposited white crystals melting from 100° to about 140°.

This product did not dissolve in concentrated hydrochloric acid, hot or cold, and could not be recrystallised to give a sharper melting point.

Quantitative hydrogenation of 2,4,2'-trinitro-4'-methoxydiphenylamine.

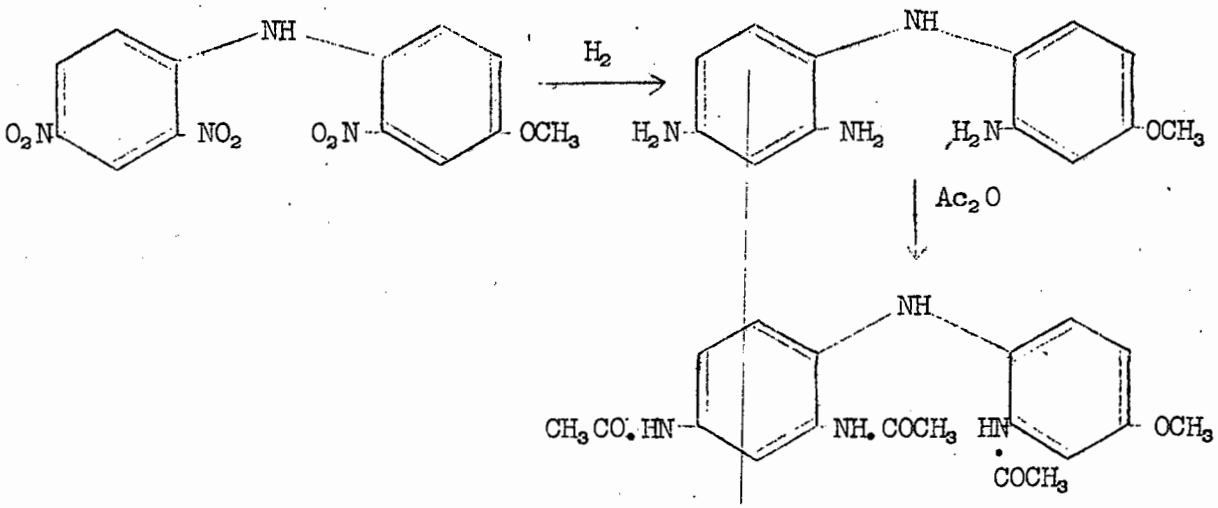



Hydrogenation of 2,4,2'-trinitro-4'-methoxydiphenylamine
Temperature 15°
Hydrogen partial pressure 732.2 mm.
Ml of H2 taken up
0
1
2
3
4
5
0
5
10
15
20
25
30
35
40
45
50
Minutes

0.0062 Gm. of 2,4,2'-trinitro-4'-methoxydiphenylamine was hydrogenated in 5 ml. of absolute alcohol in the presence of 0.0030 gm. of Adam's catalyst. The volume of hydrogen taken up was recorded with time.

From the figure illustrating hydrogen uptake with time it is seen that hydrogenation is complete after 35 minutes under the conditions of the experiment. 3.670 Ml., the volume of hydrogen taken up at N.T.P., agrees with the volume calculated, 3.741 ml., for an uptake of 9 moles of hydrogen per molecule of 2,4,2'-trinitro-4'-methoxydiphenylamine.

Preparation of 2,4,2'-triacetamido-4'-methoxydiphenylamine.



2,4,2'-Trinitro-4'-methoxydiphenylamine was hydrogenated in alcohol, the catalyst filtered off from the reddish solution under nitrogen and the alcohol evaporated from the filtrate under reduced pressure, in a nitrogen atmosphere, at room temperature. A tarry reddish residue of 2,4,2'-triamino-4'-methoxydiphenylamine was obtained, treated with a large excess of acetic anhydride and left to stand overnight. Water was added to the reaction mixture and a white oil which solidified with difficulty was obtained.

The precipitate was filtered off, washed, dried and found to have a melting point of 210° - 216°. After two recrystallisations from butanol, the butanol being washed out with ether, the melting point was constant at 215° to 216.5°.

Analysis:		C	H	N
$C_{19}H_{22}N_4O_4$	requires	61.60%	5.99%	15.12%
	Found	61.80%	6.28%	14.79%

On exposure to the atmosphere these white crystals turn pink.

Attempted oxidative ring closure of 2,4,2'-triamino-4'-methoxydiphenylamine.

[A] (i) 1.5 Gms. of 2,4,2'-trinitro-4'-methoxydiphenylamine were hydrogenated in the presence of 0.15 gm. of Adam's catalyst at 10 lbs. per sq. in., in 100 ml. of absolute alcohol, until the solution was practically colourless. The catalyst was then filtered off under nitrogen, 10 ml. of 6 N hydrochloric acid added and approximately two thirds of the alcohol evaporated off under reduced pressure, at room temperature, in a nitrogen atmosphere.

A filtered solution of 5 gms. of ferric chloride ($FeCl_3.6H_2O$) in 25 ml. of water was added and left to stand overnight. Solid matter settled out from the reddish brown solution soon after addition of the ferric chloride solution. The reaction mixture was diluted, sodium acetate added until the pH was 5 - 6, and the separated material filtered off, washed and dried. This material did not melt below 360°, and could not be recrystallised or vacuum sublimed to give a pure product.

(ii) The above hydrogenation was repeated and the ferric chloride solution added without evaporating the alcohol.

After standing for a day, the alcohol was removed under vacuum and sodium acetate added until the pH was 5 - 6. The precipitated product was filtered off, washed and dried. It had an amorphous appearance, could not be purified by recrystallisation or vacuum sublimation and did not melt below 360°.

(iii) Adding the 2,4,2'-triamino-4'-methoxydiphenylamine in acid fairly slowly to the ferric chloride solution gave a similar product.

[B] (i) 150 Mgm. of 2,4,2'-trinitro-4'-methoxydiphenylamine were hydrogenated in glacial acetic acid, the catalyst filtered off and a solution of 0.5 gms. of ferric chloride ($FeCl_3.6H_2O$) in 2.5 ml. of water added. A blue colour developed immediately, persisted for a very short period and then turned red.

After standing for a day the solution was neutralised with dilute sodium hydroxide solution and the precipitated product filtered off, washed and dried. This product did not melt below 360° and could not be purified by recrystallisation or vacuum sublimation.

Attempted atmospheric oxidative ring closure of 2,4,2'-triamino-4'-methoxydiphenylamine.

150 Mgm. of 2,4,2'-trinitro-4'-methoxydiphenylamine were hydrogenated in 10 ml. of glacial acetic acid and air bubbled through the resultant solution in the presence and absence of the catalyst.

In both cases the eventual product isolated did not melt below 360° and could not be purified by recrystallisation or vacuum sublimation.

Attempted acid ring closure of 2,4,2'-triamino-4'-methoxydiphenylamine.

(i) 1 Gm. of 2,4,2'-trinitro-4'-methoxydiphenylamine was hydrogenated as previously and the alcohol removed. The reddish tarry residue was refluxed with 6N hydrochloric acid for 2 hours.

After cooling the pH of the solution was made 5 - 6 by the addition of sodium acetate and the precipitated product filtered off, washed and dried. This product had a melting point greater than 360°. A vacuum sublimation of this product at 165° and 0.5 mm. gave an extremely small quantity of reddish sublimate. This dissolved in alkali to give an orange solution and in acid to give a blue green solution.

This product may be 2-amino-7-hydroxyphenazine. Too little was obtained for analysis.

(ii) 2 Gms. of 2,4,2'-trinitro-4'-methoxydiphenylamine were hydrogenated, the alcohol removed, the brown tarry residue taken up in 30 ml. of concentrated hydrochloric acid and heated in a sealed tube at 130° - 135° for 15 hours. A blue-green solution containing some blue-green solid resulted.

The mixture was neutralised by the addition of a sodium hydroxide solution and the precipitate filtered off and washed. The recovery was very small.

The precipitate was dissolved in approximately normal hydrochloric acid and filtered to remove any acid insolubles. With more concentrated hydrochloric acid an insoluble blue-green product - probably a hydrochloride - was formed. The

filtrate was neutralised with sodium hydroxide solution and extracted with ether. On evaporation of the slightly yellow ethereal extract a yellowish-red residue was obtained. This residue had a melting point greater than 360° and could not be purified by recrystallisation or vacuum sublimation.

Filtration of the aqueous mixture, after extraction with ether, gave a residue which did not melt below 360° and from which no sublimate could be obtained on heating at 240° and 8×10^{-2} mm.

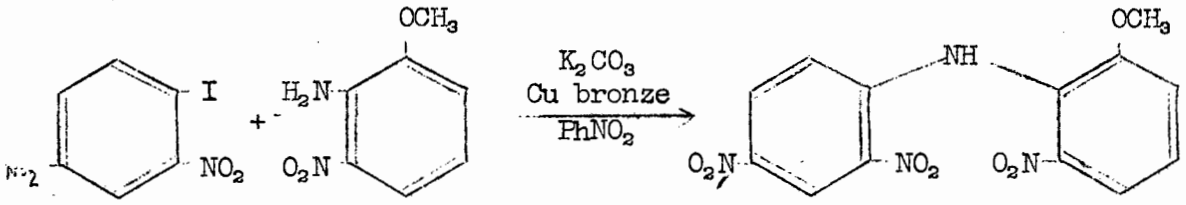
Attempted preparation of 2,2'-dinitro-4-amino-4'-methoxydiphenylamine.

(i) 0.32 Gms. of flowers of sulphur and 2.4 gms. of sodium sulphide ($Na_2S.9H_2O$) were boiled in 15 ml. of water until a clear solution resulted. This solution was slowly added to a gently boiling suspension of 3.34 gms. of 2,4,2'-trinitro-4'-methoxydiphenylamine in 100 ml. of water, with vigorous stirring. On completion of the addition, the reaction mixture was boiled for a further 20 minutes and filtered hot. The residue was found to melt at 137° - 147°. A mixed melting point with the original compound after recrystallisation from alcohol gave no depression of the melting point. Nothing separated from the filtrate.

(ii) 1.67 Gms. of 2,4,2'-trinitro-4'-methoxydiphenylamine were suspended in 60 ml. of boiling water and to this was gradually added a hot, clear solution of 1.20 gms. of sodium sulphide ($Na_2S.9H_2O$) and 0.16 gms. of sulphur, with vigorous stirring. The reaction mixture was boiled for 2¼ hours keeping the volume constant by adding water at intervals and then filtered hot. An amorphous residue was obtained which, when recrystallised from alcohol, had a melting point 137° - 150°. On doing a mixed melt with the starting material no depression of the melting point was observed.

On cooling the filtrate an extremely small amount of red material separated. This was filtered off, washed, dried and found to have a melting point 60° - 80°. This could not be recrystallised.

Preparation of 2,4,2'-trinitro-6'-methoxydiphenylamine.

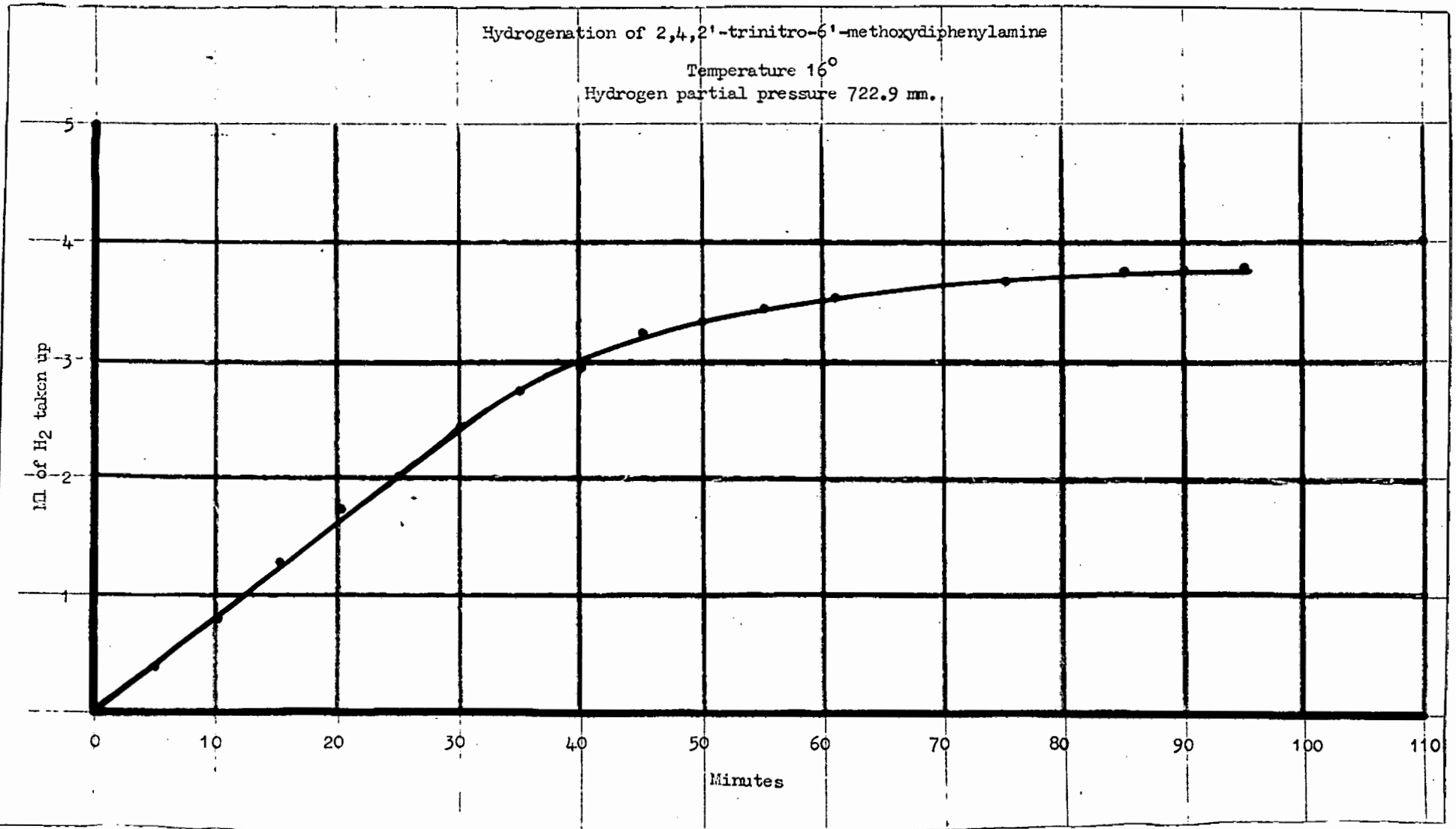


A mixture of 8.82 gms. of 2,4-dinitro-iodobenzene, 5.04 gms. of 3-nitro-o-anisidine, 6 gms. of freshly calcined potassium carbonate and 0.3 gms. of copper bronze was gently boiled in 20 ml. of nitrobenzene for 30 minutes, shaking vigorously at frequent intervals.

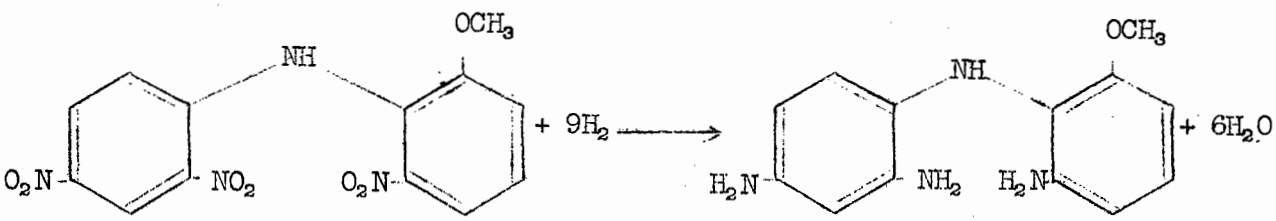
After cooling, the reaction mixture was vigorously shaken up with 175 ml. of absolute alcohol, chilled in ice, filtered and the residue washed with 50 ml. of chilled absolute alcohol. The residue was then well mixed with 60 ml. of 3N hydrochloric acid, filtered, well washed and dried. 7.5 gms. (54%) of crude 2,4,2'-trinitro-6'-methoxydiphenylamine of melting point 215° - 223° were obtained.

This was recrystallised from pyridine in the presence of a little norite to give yellow needles of melting point 222° - 225°.

Analysis:		C	H	N
$C_{13}H_{10}N_4O_7$	requires	46.43%	3.31%	16.77%
	Found	47.00%	3.22%	17.06%


Hydrogenation of 2,4,2'-trinitro-6'-methoxydiphenylamine
Temperature 16°
Hydrogen partial pressure 722.9 mm.
Ml of H2 taken up
5
4
3
2
1
0
10
20
30
40
50
60
70
80
90
100
110
Minutes

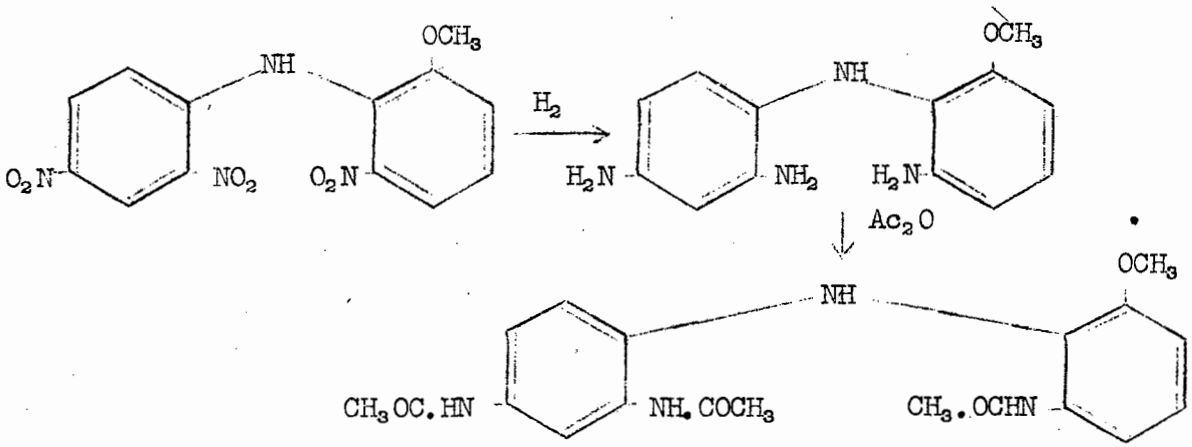
Quantitative hydrogenation of 2,4,2'-trinitro-6'-methoxydiphenylamine.



6.4 Mgm. of 2,4,2'-trinitro-6'-methoxydiphenylamine were hydrogenated in 5 ml. of absolute alcohol in the presence of 2.5 mgm. of Adam's catalyst and the hydrogen uptake recorded with time.

From the figure illustrating hydrogen uptake with time it is seen that hydrogenation is complete after about 90 minutes under these conditions.

Preparation of 2,4,2'-triacetamido-6'-methoxydiphenylamine.



1 Gm. of 2,4,2'-trinitro-6'-methoxydiphenylamine was hydrogenated at 20 lbs. per sq. in. in 60 ml. of absolute alcohol in the presence of 0.1 gm. of Adam's catalyst. The catalyst was filtered off under nitrogen and the alcohol removed under reduced pressure, at room temperature, in a nitrogen atmosphere. The residual white crystals were treated with 10 ml. of acetic anhydride, well stirred and the

reddish solution allowed to stand overnight. After standing for an hour or two white crystals separated from the solution.

An excess of water was added to the reaction mixture and the precipitated white product filtered off, washed and dried.

700 Mgm. (63%) of crude 2,4,2'-triacetamido-6'-methoxydiphenylamine of melting point 232° - 240° were obtained. Recrystallised from nitrobenzene white needles, which decompose on melting at 238° - 240°, were obtained.

Analysis:		C	H	N
$C_{19}H_{22}N_4O_4$	requires	61.60%	5.99%	15.12%
	Found	61.20%	5.71%	15.01%

Attempted oxidative ring closure of 2,4,2'-triamino-6'-methoxydiphenylamine.

1 Gm. of 2,4,2'-trinitro-6'-methoxydiphenylamine was hydrogenated, the catalyst filtered off under nitrogen and about half the alcohol evaporated off as before. 6 Ml. of 6N hydrochloric acid was added to the reddish solution, which then deepened in colour, followed by a filtered solution of 3.5 gms. of ferric chloride ($FeCl_3.6H_2O$) in 16 ml. water. The reaction mixture turned dark red, was allowed to stand overnight and the greater part of the alcohol then removed under vacuum. After slight dilution, sodium acetate was added to the residue, bringing the pH to about 5 to 6 and the precipitated product filtered off, washed and dried.

This precipitate did not melt below 360° and could not be recrystallised or vacuum sublimed.

Attempted acid ring closure of 2,4,2'-triamino-6'-methoxydiphenylamine.

(i) 10 Ml. of concentrated hydrochloric acid was added to 1 gm. of

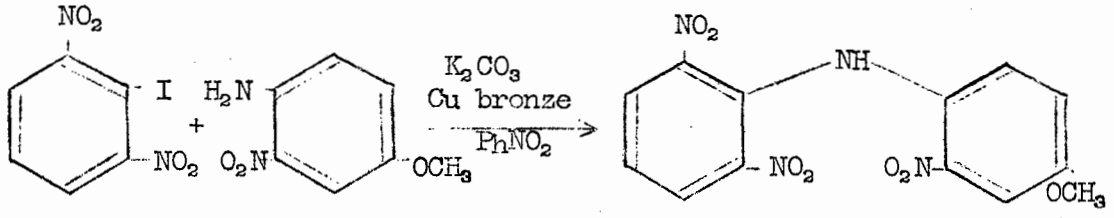
after a few recrystallisations the product still had a heterogeneous appearance. Too little product was obtained to attempt chromatographic purification.

(v) 3.36 Gms. of 3-nitro-o-anisidine, 5.88 gms. of 2,6-dinitro-iodobenzene, 8 gms. of anhydrous sodium acetate and a little copper bronze were heated together at 220° for 10 hours. Initially a sublimate passed from the reaction mixture which eventually solidified.

The reaction mixture was steam distilled, filtered and the residue washed and dried. This had a black charred appearance and did not melt below 360°.

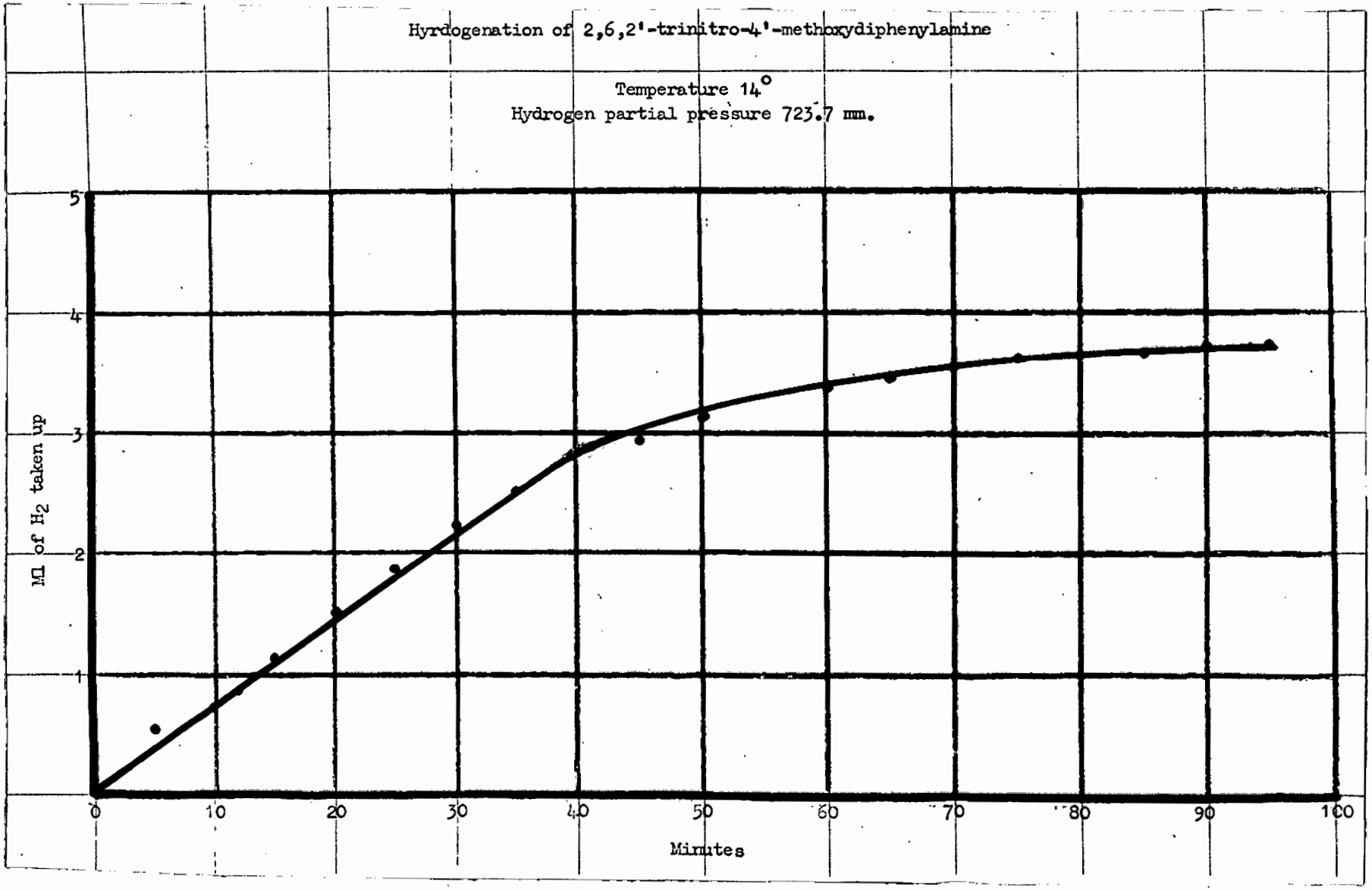
(vi) Only unchanged starting material was obtained on refluxing equimolecular portions of 3-nitro-o-anisidine and 2,6-dinitro-iodobenzene in alcohol for 4 hours.

Preparation of 2,6,2'-trinitro-4'-methoxydiphenylamine.



8.82 Gms. of 2,6-dinitro-iodobenzene, 5.04 gms. of 2-nitro -4-methoxyaniline, 6 gms. of freshly calcined potassium carbonate and 0.3 gms. of copper bronze were heated together in 20 ml. of nitrobenzene at 120° - 130° for 12 hours, shaking vigorously at frequent intervals.

After cooling the reaction mixture was shaken up with 100 ml. of alcohol, chilled, filtered and the residue washed with 50 ml. of chilled alcohol. The residue was shaken up with 60 ml. of 3 N


Hyrdogenation of 2,6,2'-trinitro-4'-methoxydiphenylamine
Temperature 14°
Hydrogen partial pressure 723.7 mm.
Ml of H2 taken up
0
1
2
3
4
5
0
10
20
30
40
50
60
70
80
90
100
Minutes

hydrochloric acid, filtered, washed and dried. On recrystallisation, from alcohol, 4.3 gms. (31%) of 2,6,2'-trinitro-4'-methoxydiphenylamine of melting point 167° - 171° were obtained. Subsequent recrystallisations raised the melting point to 168° - 171°.

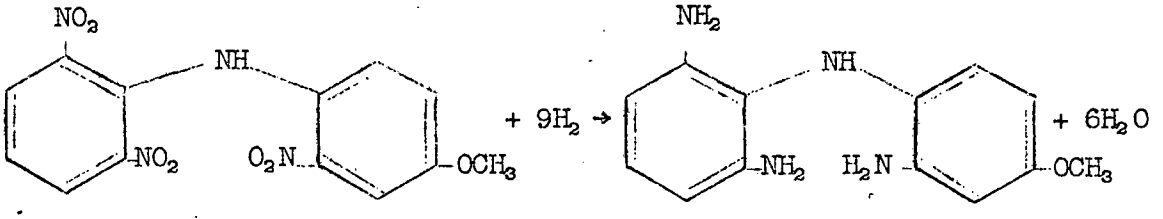
Analysis:	C	H	N
$C_{13}H_{10}N_4O_7$ requires	46.71%	3.02%	16.77%
Found	47.2%	3.09%	16.76%

Repeating this preparation, heating for only one hour, gave 2 gms. of recrystallised 2,6,2'-trinitro-4'-methoxydiphenylamine.

Heating at 155° - 160° for 90 minutes gave 5.6 gms. of charred looking material which, on recrystallisation, gave only a small recovery of the desired product.

The addition of a few drops of water to the reaction mixture did not increase the yield.

Quantitative hydrogenation of 2,6,2'-trinitro-4'-methoxydiphenylamine.

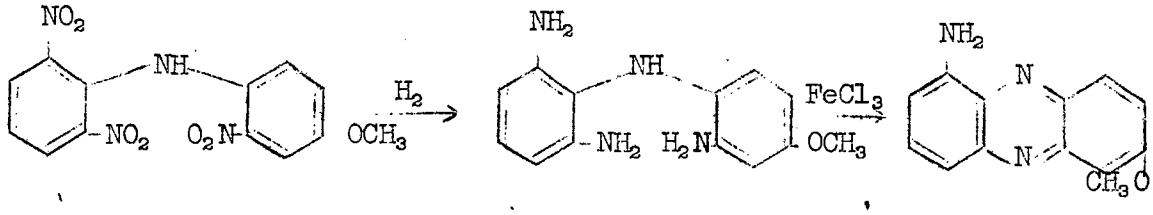


5.7 Mgm. of 2,6,2'-trinitro-4'-methoxydiphenylamine were hydrogenated in 5 ml. of absolute alcohol in the presence of 2.2 mgm. of Adam's catalyst and the hydrogen uptake recorded with time.

Vol. of H_2 taken up at N.T.P.	3.388 ml.
Theor. H_2 uptake at N.T.P.	3.438 ml.

Hydrogenation is complete after approximately 80 minutes.

Preparation of 1-amino-6-methoxyphenazine.



2 Gms. of 2,6,2'-trinitro-4'-methoxydiphenylamine were hydrogenated at 12 lbs. per sq. in. in 75 ml. of absolute alcohol in the presence of 0.1 gms. of Adam's catalyst. A slight pinkish solution with some separated triamine resulted.

10 Ml. of 6 N hydrochloric acid were added and the catalyst filtered off from the solution under suction in a nitrogen atmosphere. A filtered solution of 6.6 gms. of ferric chloride ($FeCl_3.6H_2O$) in 32 ml. of water was added to the filtrate and well shaken up. The solution turned blue green and dark crystals of what was probably the hydrochloride of 1-amino-6-methoxyphenazine separated after about 15 minutes. These crystals melted at 205° - 210° with decomposition. The reaction mixture was left to stand for a day and then some of the alcohol evaporated off under reduced pressure. Sodium acetate was added to the residue until the pH was 5 - 6. The separated reddish precipitate was filtered off, washed with a little sodium acetate solution, then with water, dried and found to have a melting point 156° - 162°.

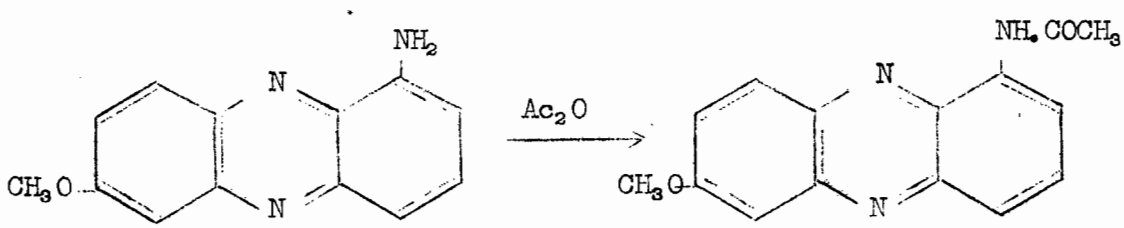
Recrystallised from petroleum ether (b. pt. 80° - 100°) 1 gm. (75%) of 1-amino-6-methoxyphenazine of melting point 165° - 170° was recovered. Further recrystallisations raised the melting point to 168° - 171°.

Analysis:	C	H	N
$C_{13}H_{11}N_3O$ requires	69.31%	4.92%	18.66%
Found	69.60%	5.24%	18.84%

These orange needles have a bright orange-yellow fluorescence. In concentrated hydrochloric acid, a yellowish solution is obtained, going blue-green on dilution. This compound may also be recrystallised from water.

A slightly better yield was obtained in this preparation by evaporating all the alcohol off under nitrogen, after removal of the catalyst, adding 75 ml. of water and then the ferric chloride solution.

Preparation of 1-acetamido-6-methoxyphenazine.



300 Mgm. of 1-amino-6-methoxyphenazine were treated with 8 ml. of acetic anhydride and allowed to stand at room temperature for 36 hours, stirring occasionally.

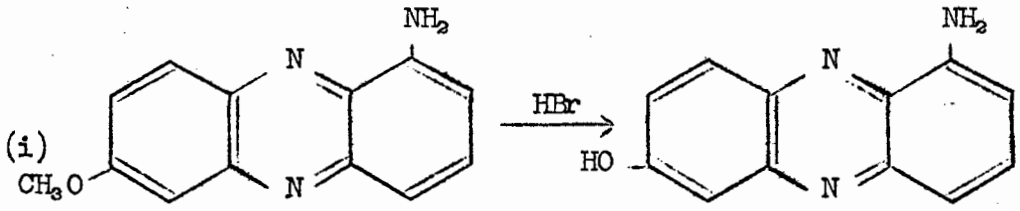
The reaction mixture was poured into water, the precipitated product filtered off, washed and dried. About 400 mgm. (100%) of crude 1-acetamido-6-methoxyphenazine of melting point 217° - 223° were obtained. Recrystallised from alcohol the melting point was raised to 222° - 225°.

Analysis:		C	H	N
$C_{15}H_{13}N_3O_2$	requires	67.41%	4.90%	15.72%
	Found	67.8%	5.27%	15.50%

These very light yellow needles have a bright yellow fluorescence. Dissolved in concentrated hydrochloric acid a red solution is obtained which loses intensity on dilution. By heating with dilute hydrochloric

acid the compound is hydrolysed and a blue green solution is obtained.

Preparation of 1-amino-6-hydroxyphenazine.



0.2 Gms. of 1-amino-6-methoxyphenazine was refluxed for 3 hours with 4.5 ml. of 48% hydrobromic acid. On cooling, dark, dense crystals, possibly the hydrobromide of 1-amino-6-hydroxyphenazine, separated. The reaction mixture was diluted, made alkaline by the addition of sodium hydroxide solution and filtered.

By the addition of hydrochloric acid the pH of the filtrate was adjusted to about 6, the precipitated product filtered off, washed and dried.

Approximately 0.2 gms. of crude 1-amino-6-hydroxyphenazine was obtained. On heating slowly this product did not melt below 360°, but appeared to be undergoing decomposition from about 220°; however, on heating rapidly, a melting point of 250° - 258° was observed.

Fine long orange needles were obtained by recrystallisation from water. After drying over calcium chloride the crystals turned red.

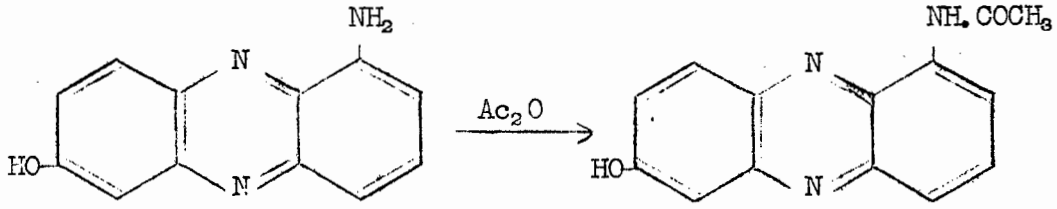
Recovery was only 90 - 100 mgm. (40% - 50%). Recrystallised again, on rapid heating 1-amino-6-hydroxyphenazine started decomposing at about 260° and melted sharply with decomposition at 270°.

Analysis:	C	H	N
$C_{12}H_9N_3O$ requires	68.23%	4.30%	19.89%
Found	68.20%	4.31%	19.46%

1-Amino-6-hydroxyphenazine dissolves in acetone to give a blue-green solution, in concentrated hydrochloric acid to give a yellowish solution turning blue-green on dilution and in alkali to give a red solution with a reddish fluorescence. These crystals have no noticeable fluorescence.

(ii) A small amount of 1-amino-6-hydroxyphenazine was obtained by refluxing 1-amino-6-methoxyphenazine with concentrated hydrochloric acid for 2 hours.

Preparation of 1-acetamido-6-hydroxyphenazine.



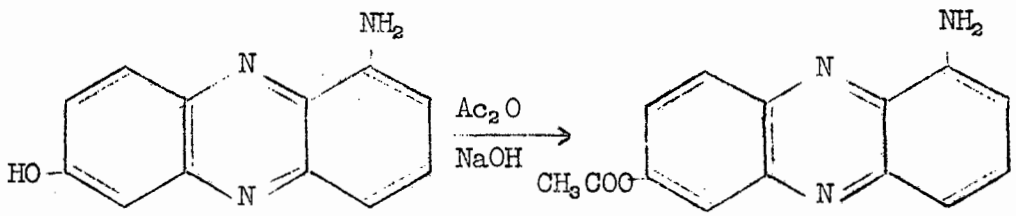
150 Mgm. of 1-amino-6-hydroxyphenazine were shaken up with 10 ml. of acetic anhydride and left to stand at room temperature for a day. The reaction mixture was then poured into approximately 100 ml. of water. The yellow precipitate was filtered off, washed and dried.

150 Mgm. (83%) of crude 1-acetamido-6-hydroxyphenazine, melting at 294° - 302° with decomposition, was obtained. This was recrystallised from butanol in the presence of a little norite to give fine yellow needles. On heating these crystals showed slight signs of melting from 285° and melted rapidly at 297° - 299° with decomposition, decomposition apparently starting with the initial melting. Recrystallised again, there were slight signs of decomposition from 280° and rapid melting with decomposition at 297°.

Analysis:		C	H	N
$C_{14}H_{11}N_3O_2$	requires	66.37%	4.38%	16.59%
	Found	66.2%	4.57%	15.90%

1-Acetamido-6-hydroxyphenazine has a very slight dirty yellow fluorescence. It dissolves readily in alkali to give an orange solution with an orange fluorescence, and in concentrated hydrochloric acid to give a red solution, not changing in colour on dilution.

Preparation of 1-amino-6-acetoxyphenazine.



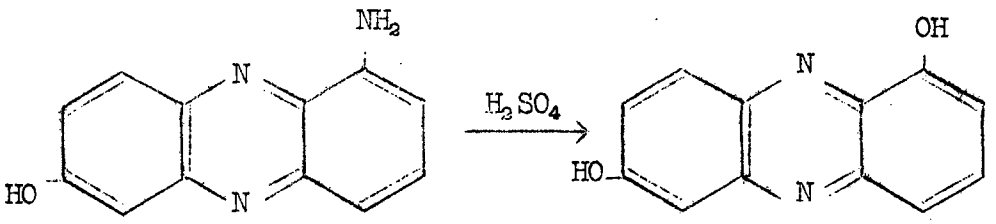
200 Mgm. of 1-amino-6-hydroxyphenazine were dissolved in 2 ml. of water containing 110 mgm. of sodium hydroxide, chilled in ice and approximately 1 - 2 gms. of finely crushed ice added. 0.24 Gm. of acetic anhydride was then added in one portion with vigorous shaking, keeping the mixture well cooled.

The dark red solution rapidly changed colour and an orange precipitate separated. This reaction mixture was left in the ice bath for a further 30 minutes, stirring occasionally, then filtered and the orange residue well washed and dried.

200 Mgm. (83%) of crude 1-amino-6-acetoxyphenazine of melting point 168° - 176° were obtained. This was recrystallised from alcohol to a melting point of 182° - 185°.

Analysis:		C	H	N
$C_{14}H_{11}N_3O_2$	requires	66.37%	4.38%	16.59%
	Found	66.78%	4.46%	16.34%

Conversion of 1-amino-6-hydroxyphenazine to 1,6-dihydroxyphenazine.



500 Mgm. of 1-amino-6-hydroxyphenazine were heated for 18 hours at 150° with 25 ml. of 3 N sulphuric acid in a sealed tube with occasional shaking.

After cooling the reaction mixture was neutralised by the addition of a sodium hydroxide solution and the precipitated product filtered off, washed and dried. The product was vacuum sublimed at 250° at 0.1 mm., giving a darkish sublimate, which turned brown-yellow with time. On heating, this product decomposed at 305° in an open tube and at 303° in a sealed tube. This agrees with the melting point given by Serebryanyi[43] for 1,6-dihydroxyphenazine. Too little of the product was obtained for analysis. 1,6-dihydroxyphenazine dissolves in alkaline solution to give a red solution and in hydrochloric acid to give a golden coloured solution.

SECTION IIIB.

Attempted preparation of 2-nitrophenazine.

(i) 5 Gms. of 2,4-dinitrodiphenylamine, 7 gms. of ferrous oxalate ($FeC_2O_4.2H_2O$) and 50 gms. of granulated lead were intimately mixed and then heated on an oil bath at 280° - 290° for 40 minutes. There was an initial vigorous reaction during which vapours sublimed from the reaction flask into a condenser on the flask. A strong isocyanide smell was noticeable in the reaction mixture on completion of the heating.

The sublimate and the reaction mixture were extracted with ether and the ether then evaporated. The residue was vacuum sublimed to give orange needles of melting point 134° - 144° and fine red needles of melting point 140° - 150°. Only an extremely small amount of sublimate was obtained.

The sublimate dissolved in concentrated hydrochloric acid to give a blue-green solution turning red on dilution just as is the case with 2-aminophenazine.

A paper chromatogram of the sublimate compared with 2-aminophenazine using

(i) Butanol : conc. hydrochloric acid = 2 : 1 satd. with water
(ii) " : " " " = 8 : 1 " " "
(iii) " : " " " = 1 : 1 " " "

as solvents showed the presence in the sublimate of 2-aminophenazine.

The sublimate was shaken up with concentrated hydrochloric acid and filtered. The residue was found to be unchanged 2,4-dinitrodiphenylamine. On neutralisation of the filtrate with sodium hydroxide solution a precipitate of melting point 218° - 227° was obtained. This was recrystallised from

alcohol to give light yellow needles of melting point of 224° - 227°.

Analysis:		C	H	N
$C_{12}H_7N_3O_2$	requires	63.98%	3.13%	18.65%
	Found	64.91%	3.10%	18.53%

This product is apparently 2-nitrophenazine. Kehrmann and Havas[52] quote a m. pt. of 214° for 2-nitrophenazine as compared to 224° - 227° found here. On admixture with (ii), (a) below no depression of the m. pt. was observed.

Dissolved in concentrated hydrochloric acid a yellow-green solution, from which it was precipitated on dilution, was obtained.

(ii) This preparation was repeated, the sublimate dissolved in dry benzene, passed through an alumina column and eluted with dry benzene. The chromatogram developed consisted of four bands:

(a) A broad frontal light yellow band which on elution and evaporation of the benzene deposited yellow crystals of melting point 200° - 208° which were recrystallised from alcohol to a melting point 224° - 227°.

(b) Secondly, a distinct narrow purple band, which on elution and evaporation of the benzene left a small purplish deposit (not enough for a melting point). This residue, dissolved in concentrated hydrochloric acid, gave a blue-green solution, turning red on dilution, just as with 2-aminophenazine.

Using butanol : conc. HCl = 2 : 1 satd. with water
" : " HCl = 8 : 1 " " "
" : " HCl = 1 : 1 " " "

as solvents, the residue showed the same movement as 2-aminophenazine on a paper chromatogram.

(c) Thirdly, a small orange band, and

(d) After a small separation, a last small orange band with bright orange fluorescence.

Attempted preparation of 2-nitro-7-methoxyphenazine.

(i) 5 Gms. of 2,4-dinitro-4'-methoxydiphenylamine, 6.5 gms. of ferrous oxalate ($FeC_2O_4.2H_2O$) and 50 gms. of granulated lead were intimately mixed and heated on an oil bath, at 280° - 290°. After an initial vigorous reaction, heating was continued for 40 minutes. During the initial vigorous reaction there was copious evolution of vapours which sublimed on to a condenser placed on the reaction flask.

The reaction mixture and sublimate were extracted with ether and the ether then extracted with 6 N hydrochloric acid. On evaporation of the ether a large amount of starting material was isolated.

The acid extract was neutralised with 6 N sodium hydroxide solution and then extracted with ether. On evaporation of the ether an extremely small amount of dark residue of melting point 95° - 120° was left behind. This residue dissolved in concentrated hydrochloric acid gave a blue-green solution, turning red on dilution, just as is the case with 2-aminophenazine.

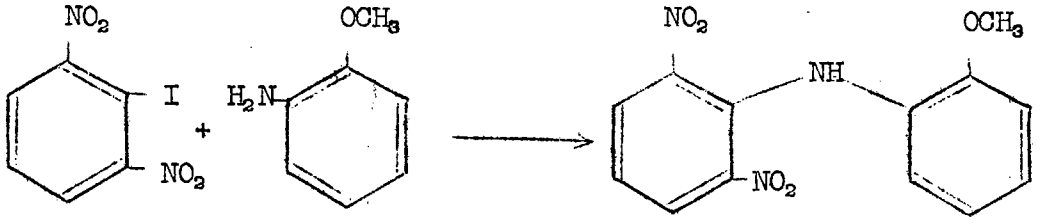
This residue was dissolved in dry benzene passed through an alumina column and eluted with dry benzene. The chromatogram developed consisted of a distinct small purple band followed by a number of less significant orange bands.

On elution of the purple band and evaporation of the benzene, a dark residue was obtained. Placed on paper and compared with 2-aminophenazine using

(i) butanol : concentrated hydrochloric acid = 2:1 saturated with water, and

(ii) butanol : concentrated hydrochloric acid = 4:1 saturated with water, as eluting solvents, no separation of the spots was observed.

Preparation of 2,6-dinitro-2'-methoxydiphenylamine.



5.88 Gms. of 2,6-dinitro-iodobenzene and 2.46 gms. of o-anisidine were refluxed in 20 ml. of 96% alcohol for 4 hours. On cooling a dark red mass of crystals separated and was filtered off. 4.5 Gms. (54%) of 2,6-dinitro-2'-methoxydiphenylamine of melting point 145° - 157° was obtained. This was recrystallised from alcohol in the presence of a little norite to give bright red needles of melting point 161° - 164°.

Analysis:		C	H	N
$C_{13}H_{11}N_3O_5$	requires	53.98%	3.83%	14.53%
	Found	54.4%	3.63%	14.30%

Attempted mono-reduction of 2,6-dinitro-2'-methoxydiphenylamine.

(i) Sodium polysulphide as reducing agent:

0.7 Gm. of flowers of sulphur and 2.6 gms. of sodium sulphide ($Na_2S.9H_2O$) were boiled in 12 ml. of water until a clear solution resulted. This solution was then added gradually, from a dropping funnel, over a period of minutes to a gently boiling suspension of 2.89 gms. of 2,6-dinitro-2'-methoxydiphenylamine, in 75 ml. of water, with vigorous stirring. On completion of the addition the reaction mixture was boiled for a further 20 minutes and then filtered hot. The residue was found to be unchanged 2,6-dinitro-2'-methoxydiphenylamine.

No product could be isolated from the filtrate.

(ii) Aqueous stannous chloride as reducing agent:

2.2 Gms. of tin were boiled in concentrated hydrochloric acid until solution was complete and the volume brought to 40 ml. by addition of more concentrated hydrochloric acid. With the stannous chloride-hydrochloric acid solution at 40°, 2.89 gms. of 2,6-dinitro-2'-methoxydiphenylamine were added in one portion, with vigorous stirring. The reaction mixture was then slowly heated to 85° on a water-bath, maintained at this temperature for 1 hour, cooled for an hour and then heated at 85° for a further 3 hours.

The reaction mixture was cooled and filtered. Unchanged 2,6-dinitro-2'-methoxydiphenylamine was filtered off in large quantity.

6 N sodium hydroxide solution was added to the filtrate until it was strongly alkaline and the precipitated product filtered off, washed and dried. Approximately 0.7 gms. (31%) of crude 2,6-diamino-2'-methoxydiphenylamine of melting point 146° - 153° was isolated. This crude product was recrystallised from alcohol in the presence of a little norite. The white needles of 2,6-diamino-2'-methoxydiphenylamine, on heating, showed signs of softening at 150° and melted at 155° - 158°.

Analysis:	C	H	N
$C_{13}H_{15}N_3O$ requires	68.08%	6.60%	18.32%
Found	68.24%	6.61%	17.84%

Selective mono-reduction was not effected in this reduction. Both nitro groups were reduced in poor yield.

(iii) Alcoholic stannous chloride as reducing agent:

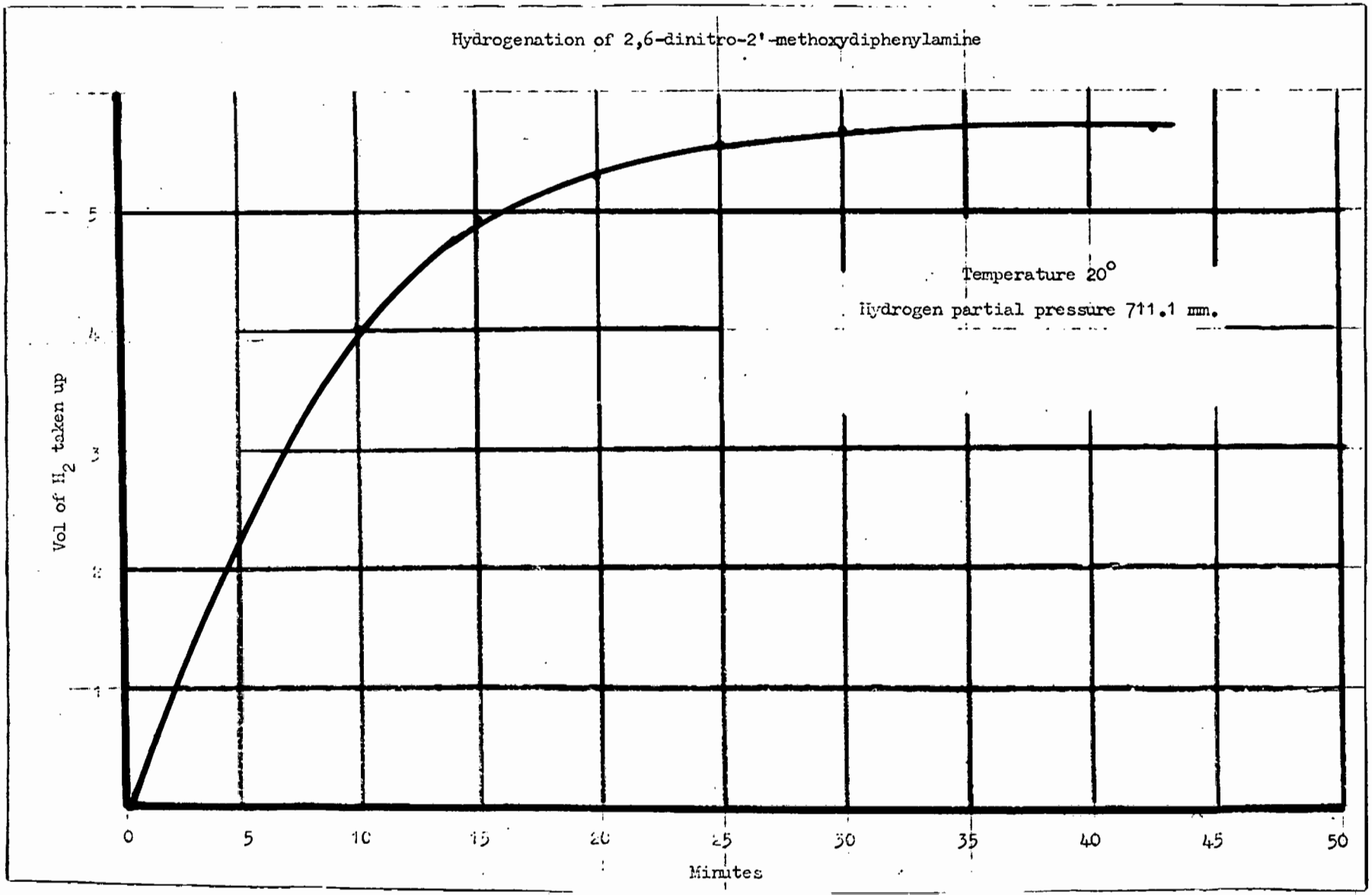
50 Ml. of absolute alcohol were saturated with dry hydrochloric acid gas. 7.1 Gms. of stannous chloride ($SnCl_2.2H_2O$) were then dissolved in this solution and then added in one portion to a suspension of 2.89 gms. of 2,6-dinitro-2'-methoxydiphenylamine in 100 ml. of absolute alcohol at room temperature. The reaction mixture was refluxed for 3 hours, allowed to stand for a day and the alcohol then distilled off.

The residue was diluted to approximately 150 ml., made strongly alkaline by the addition of a 6 N sodium hydroxide solution and the dark precipitated product filtered off, washed and dried. 2.3 Gms. of this material of melting point 105° - 115° were obtained. This product was extracted with ether and the ether evaporated to give a dirty red residue of melting point 110° - 190°. On extraction of this residue with 6 N hydrochloric acid and neutralisation of the extract with 6 N sodium hydroxide solution a reddish product of melting point 135° - 200° was filtered off. This product could not be purified by recrystallisation.

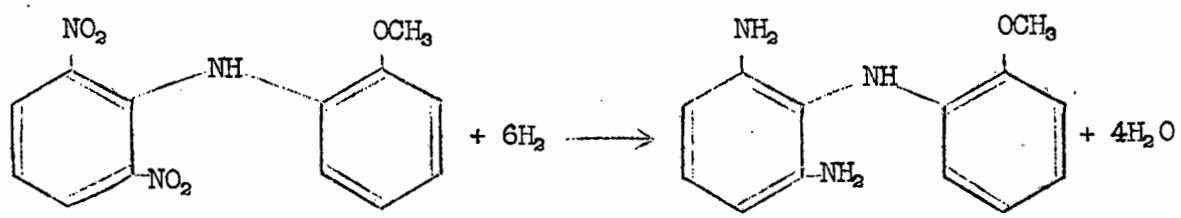
This material was placed on chromatographic paper and then developed with butanol/conc. hydrochloric acid = 4/1 saturated with water as solvent. Four spots with R_F values 0.43, 0.67, 0.85 and one at the solvent front were observed.

With butanol saturated with ammonia solution as solvent, a fairly distinct spot with R_F value 0.93 was followed by a tail.

With butanol/water/acetic acid = 5/4/1 as solvent, a spot with R_F value 0.91 was followed by a long tail.


Hydrogenation of 2,6-dinitro-2'-methoxydiphenylamine
Temperature 20°
Hydrogen partial pressure 711.1 mm.
Vol of H_2 taken up
0
5
10
15
20
25
30
35
40
45
50
Minutes

Quantitative hydrogenation of 2,6-dinitro-2'-methoxydiphenylamine.

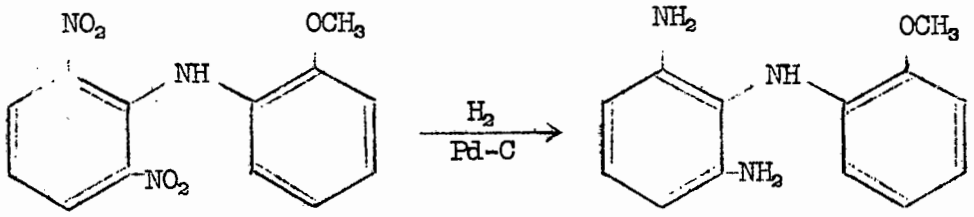


10.82 Mgm. of 2,6-dinitro-2'-methoxydiphenylamine were hydrogenated in 5 ml. of absolute alcohol in the presence of 3 mgm. of palladium-charcoal catalyst and the hydrogen uptake recorded with time.

Vol. of H_2 taken up at N.T.P.	4.944 ml.
Theor. H_2 uptake at N.T.P.	5.028 ml.

From the figure illustrating hydrogen uptake with time it is seen that under these conditions the hydrogenation is complete after approximately 30 minutes.

Preparation of 2,6-diamino-2'-methoxydiphenylamine.

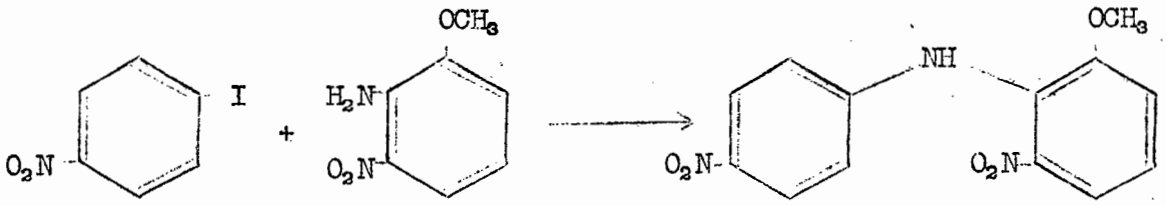


2 Gms. of 2,6-dinitro-2'-methoxydiphenylamine were hydrogenated in 150 ml. of absolute alcohol in the presence of 0.1 gms. of palladium-charcoal catalyst at 40 lbs. per sq. in. until the solution was colourless. White crystals of 2,6-diamino-2'-methoxydiphenylamine separated from the solution.

in 12.5 ml. of nitrobenzene for 30 minutes.

(iv) No condensation took place on refluxing 2.49 gms. of p-iodonitrobenzene and 1.68 gms. of 3-nitro-o-anisidine in 30 ml. of 96% alcohol for 4 hours.

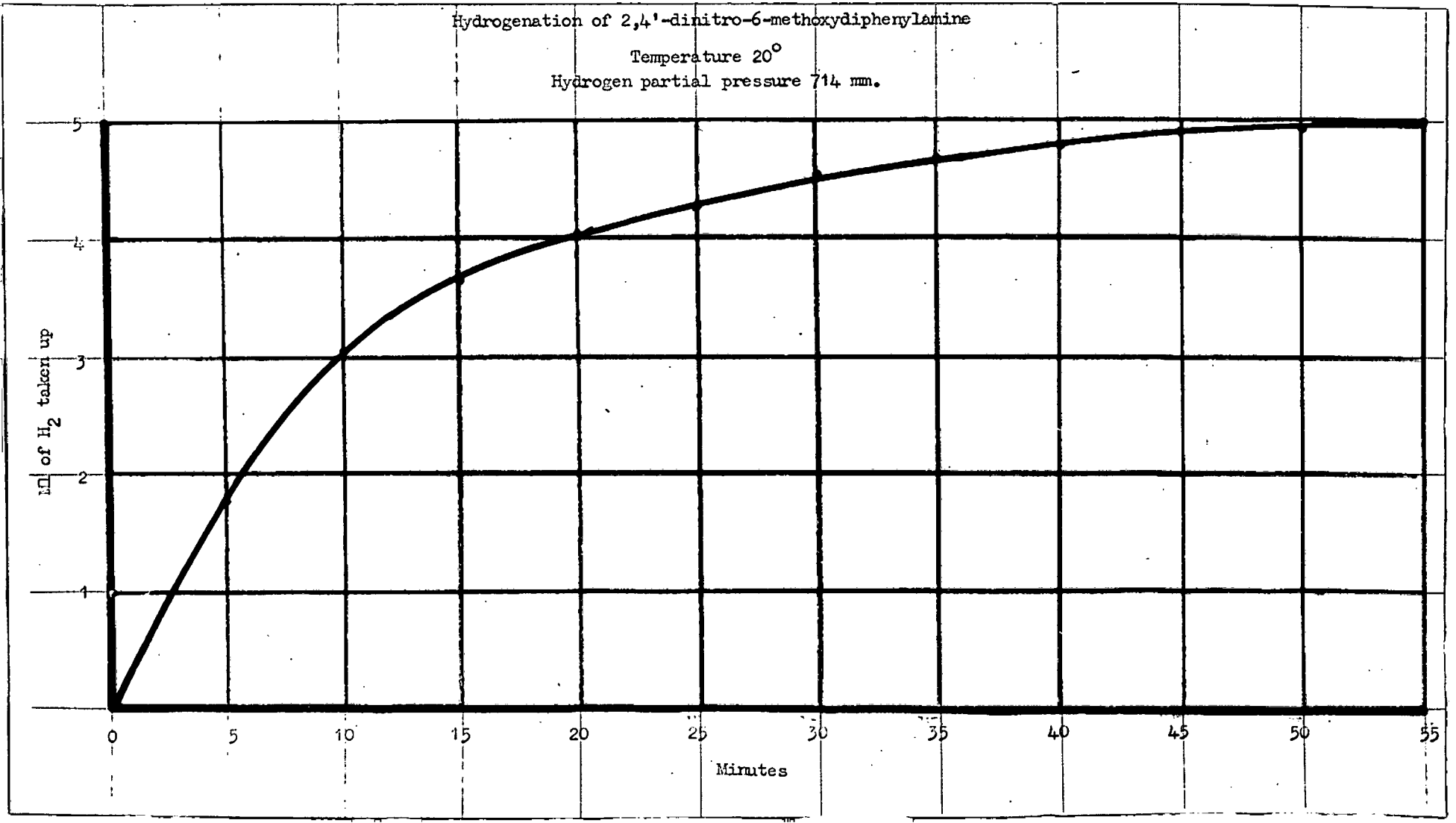
Preparation of 2,4'-dinitro-6-methoxydiphenylamine.



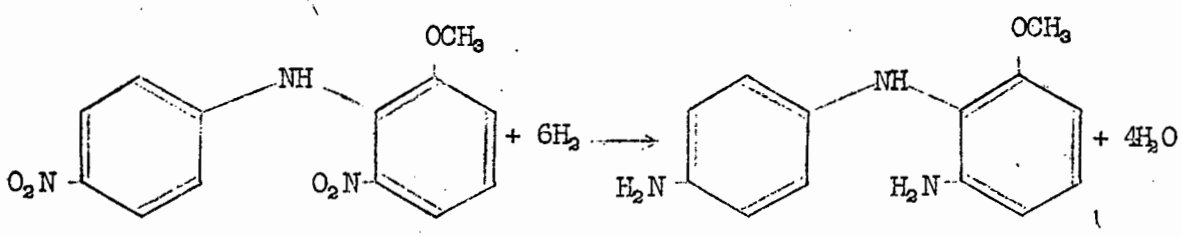
11.41 Gms. of p-iodonitrobenzene, 7.7 gms. of 3-nitro-o-anisidine, 5.7 gms. of calcined potassium carbonate and 1.1 gms. of copper bronze were heated to gentle boiling in 32 ml. of nitrobenzene for 40 minutes. The reaction mixture was steam distilled, filtered and the residue well washed, dried and recrystallised from xylene to give 6.5 gms. (49%) of orange-red fern shaped clusters of needles of 2,4'-dinitro-6-methoxydiphenylamine which soften at 140° and melt at 144° - 148°.

After five recrystallisations from toluene, the first recrystallisation being done in the presence of a little norite, the crystals softened at 147° and melted at 150° - 152°.

Analysis:		C	H	N
$C_{13}H_{11}N_3O_5$	requires	53.98%	3.83%	14.53%
	Found	54.20%	3.81%	14.35%


Hydrogenation of 2,4'-dinitro-6-methoxydiphenylamine
Temperature 20°
Hydrogen partial pressure 714 mm.
Ml of H2 taken up
5
4
3
2
1
0
5
10
15
20
25
30
35
40
45
50
55
Minutes

Quantitative hydrogenation of 2,4'-dinitro-6-methoxydiphenylamine.

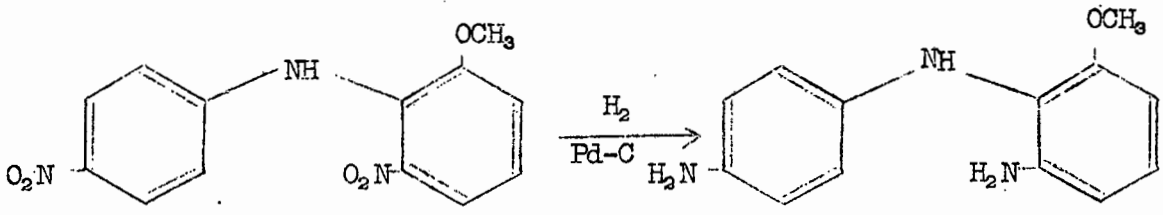


9.90 Mgm. of 2,4'-dinitro-6-methoxydiphenylamine were hydrogenated in 5 ml. of absolute alcohol in the presence of 3 mgm. of palladium-charcoal catalyst and the hydrogen uptake recorded with time.

Vol. of H_2 taken up at N.T.P.	4.466 ml.
Theor. H_2 uptake at N.T.P.	4.600 ml.

From the graph it is evident that under these conditions hydrogenation is complete after approximately 50 minutes.

Preparation of 2,4'-diamino-6-methoxydiphenylamine.

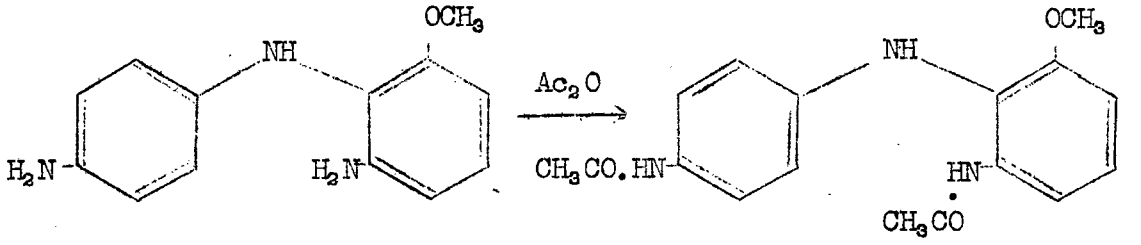


2 Gms. of 2,4'-dinitro-6-methoxydiphenylamine were hydrogenated in 150 ml. of absolute alcohol at 40 lbs. per sq. in. in the presence of 0.1 gm. of palladium-charcoal catalyst until the solution was practically colourless.

The alcohol was then evaporated at about 40° under reduced pressure in a nitrogen atmosphere. A tarry residue which solidified with difficulty was obtained. No attempt was made to recrystallise

the crude 2,4'-diamino-6-methoxydiphenylamine.

Preparation of 2,4'-diacetamido-6-methoxydiphenylamine.



The crude product from the above hydrogenation was treated with a large excess of acetic anhydride. There was an initial rise in temperature and after shaking for a few minutes a thick white precipitate separated. After standing at room temperature for 6 hours the reaction mixture was poured into about 400 ml. of water and the precipitated white product filtered off, washed and dried. 1.5 Gms. (69%) of crude 2,4'-diacetamido-6-methoxydiphenylamine of melting point 190° - 194° were obtained. This was recrystallised from alcohol to give white needles of melting point 202° - 204°.

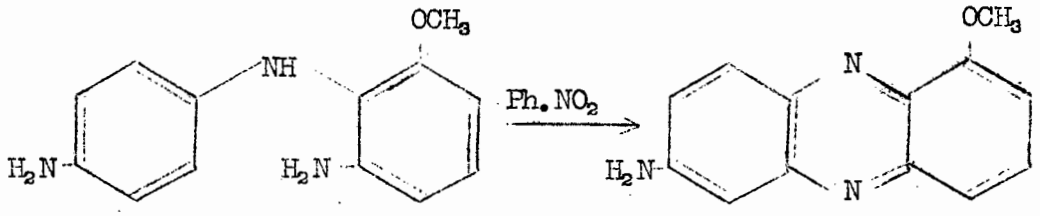
Analysis:		C	H	N
$C_{17}H_{19}N_3O_3$	requires	65.80%	5.20%	13.54%
	Found	65.53%	5.94%	13.46%.

Attempted preparation of 1-methoxy-6-aminophenazine.

(i) 2,4'-Diamino-6-methoxydiphenylamine was boiled in a 4% potassium chromate, 10% sulphuric acid solution for about 30 minutes, cooled and the reaction mixture made alkaline. The precipitate was filtered off, washed and dried. This product could not be purified by vacuum sublimation or recrystallisation.

(ii) 2 Gms. of 2,4'-diamino-6-methoxydiphenylamine were shaken up in about 100 ml. of dry ether with a large excess of powdered silver oxide and anhydrous sodium sulphate and then left to stand overnight. The reaction mixture was filtered, 60 ml. of 2 N hydrochloric acid added to the filtrate and then heated on a water-bath for 5 hours. After cooling the solution was neutralised and the precipitated product filtered off, washed and dried. This product could not be purified by recrystallisation or vacuum sublimation.

Preparation of 1-methoxy-6-aminophenazine.



1 Gm. of 2,4'-diamino-6-methoxydiphenylamine and a little m-dinitrobenzene were refluxed in about 40 ml. of nitrobenzene for 5 hours. After cooling, about 60 ml. of 5 N hydrochloric acid was added to the solution and then steam distilled to remove the nitrobenzene. The residue after steam distilling was cooled, made just alkaline and the precipitated product filtered off, washed and dried. This crude 1-methoxy-6-aminophenazine showed slight signs of melting from about 150° and melted at 249° - 256°.

Recrystallised from water 400 mgm. (40%) of orange needles of melting point 269° - 277° were obtained. 1-Methoxy-6-aminophenazine was recrystallised to a melting point of 278° - 281°.

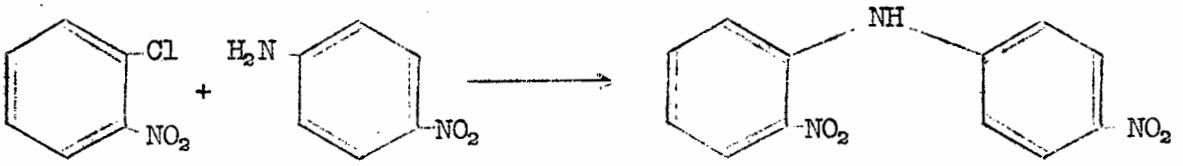
Analysis:	C	H	N
$C_{13}H_{11}N_3O.2H_2O$ requires	59.74%	5.79%	16.08%
Found	60.37%	5.50%	16.19%
$C_{13}H_{11}N_3O$ requires	69.31%	4.92%	18.65%
Found after drying at 110° in vacuo	69.31%	5.07%	18.33%

1-Methoxy-6-aminophenazine recrystallised from water has 2 molecules of water of crystallisation.

1-Methoxy-6-aminophenazine has an orange fluoresence. Dissolved in concentrated hydrochloric acid a purple solution is obtained, turning red on dilution.

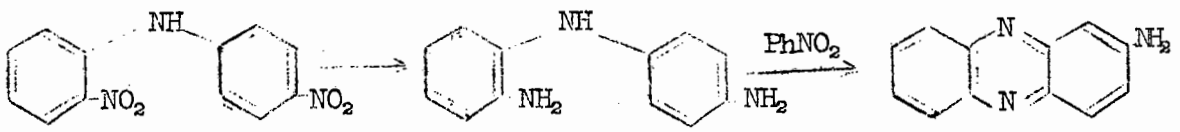
Preparation of 2,4'-dinitrodiphenylamine.

A.R. Katzitzky and S.G. Plant. J.C.S. 412 (1953).



A 49% yield of 2,4'-dinitrodiphenylamine (m. pt. 217° - 220°) was obtained.

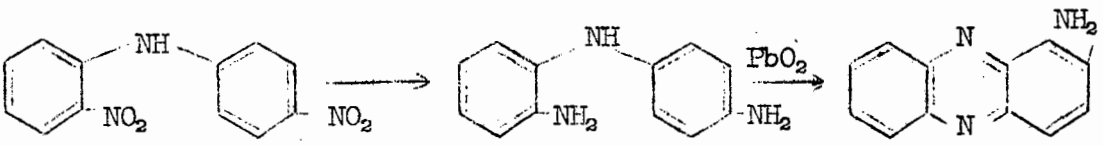
Preparation of 2-aminophenazine from 2,4'-diaminodiphenylamine.



1 Gm. of 2,4'-dinitrodiphenylamine was hydrogenated at 40 lbs. per sq. in. in 75 ml. of absolute alcohol in the presence of 0.05 gms. of palladium-charcoal catalyst until the solution was practically colourless. The alcohol was evaporated in a nitrogen atmosphere under reduced pressure at about 40° leaving 2,4'-diaminodiphenylamine as a dark tar.

(i) A little m-dinitrobenzene was added to the diphenylamine and then refluxed for 4 hours in 50 ml. of nitrobenzene. After cooling, about 100 ml. of 5 N hydrochloric acid was added and the mixture steam distilled to remove the nitrobenzene. The residue after steam distillation was made just alkaline, the precipitated product filtered off, washed and dried. 0.7 Gm. (70%) of crude 2-aminophenazine of melting point 260° - 270° was obtained. After recrystallisation from a 50% aqueous-alcoholic solution (recovery was poor) no depression of the melting point was observed on admixture with a sample of previously prepared 2-aminophenazine.

(ii)

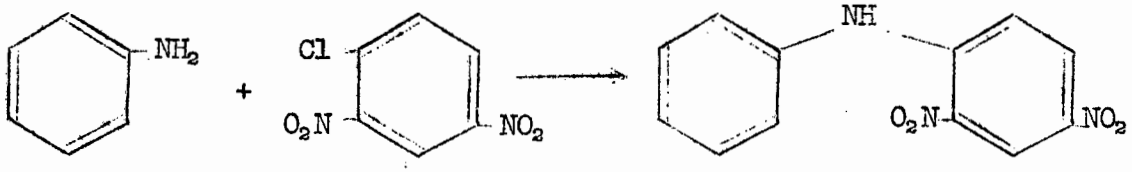


1 Gm. of 2,4'-diaminodiphenylamine was refluxed for 1 hour with 15 gms. of powdered lead dioxide in 50 ml. of xylene. The hot reaction mixture was filtered and the residue washed with a little hot xylene. The combined filtrate and washings were extracted with 6 N hydrochloric acid, the extract made just alkaline and the precipitate filtered off, washed and dried. A small yield of 2-aminophenazine was obtained on recrystallisation from a 50% aqueous-alcoholic solution.

A mixed melting point of this product with previously prepared 2-aminophenazine gave no depression of the melting point.

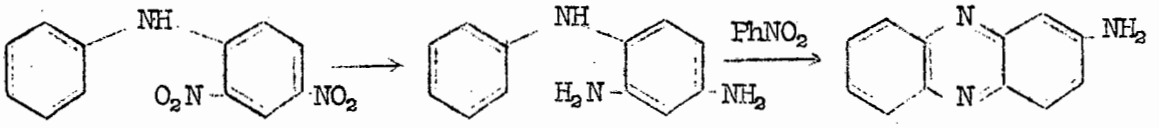
Preparation of 2,4-dinitrodiphenylamine.

Hickinbottom. Reactions of Org. Compounds, p.271.



Equimolecular proportions of aniline and 2,4-dinitrochlorobenzene were heated together on a water-bath for about 20 minutes. The resulting solid red mass was recrystallised from alcohol to give a 50% yield of red needles of 2,4-dinitrodiphenylamine of melting point 155° - 157°.

Preparation of 2-aminophenazine from 2,4-diaminodiphenylamine.

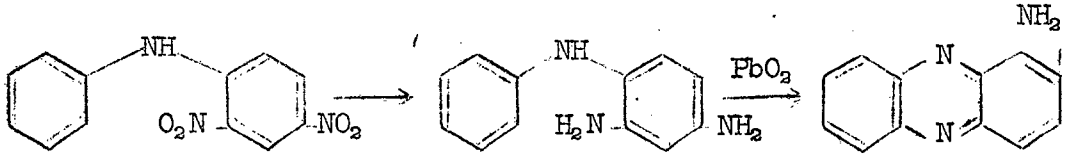


1 Gm. of 2,4-dinitrodiphenylamine was hydrogenated in 75 ml. of absolute alcohol at 30 lbs. per sq. in. in the presence of 0.05 gm. of palladium-charcoal catalyst until the solution was practically colourless. The alcohol was then evaporated under reduced pressure in a nitrogen atmosphere at about 40° leaving white crystals of 2,4-diaminodiphenylamine.

(i) A little m-dinitrobenzene was added to the crystals and then refluxed for 4½ hours in 50 ml. of nitrobenzene. After cooling approximately 70 ml. of 6 N hydrochloric acid were

added to the solution and the nitrobenzene then removed by steam distillation. The cooled residue was filtered and the filtrate made just alkaline. A brownish precipitate was filtered off, washed, dried and found to have a melting point of 180° - 240°. This product was vacuum sublimed at a maximum temperature of 280° at 7 x 10^{-2} mm. to give a small amount of red sublimate of melting point 260° - 270° softening from 210°. Recrystallised from a 50% aqueous alcoholic solution, 50 mgm. (5%) of 2-aminophenazine of melting point 277° - 280° was obtained. No depression of the melting point was observed on admixture with 2-aminophenazine.

(ii)

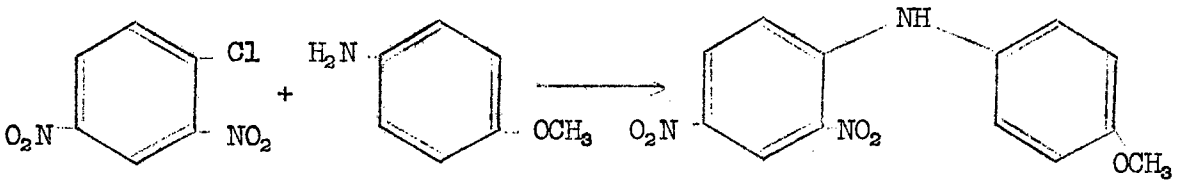


1.5 Gms. of 2,4-diaminodiphenylamine were refluxed for 1 hour with 20 gms. of powdered lead dioxide in 65 ml. of xylene. The lead dioxide was filtered off from the hot solution and washed with a little hot xylene. The combined filtrate and washings were extracted with 6 N hydrochloric acid, the acid extract filtered, made just alkaline and the precipitate filtered off, washed and dried.

0.2 Gm. (13%) of crude 2-aminophenazine of melting point 265° - 270° was obtained. After recrystallisation from a 50% aqueous-alcoholic solution, the red crystals, of melting point 267° - 271°, obtained, gave no depression of the melting point on admixture with a sample of 2-aminophenazine.

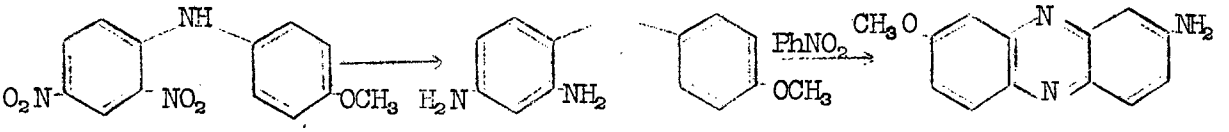
Preparation of 2,4-dinitro-4'-methoxydiphenylamine.

Compare O. Fisher. Ber. 29, 1875.



A 55% yield of 2,4-dinitro-4'-methoxydiphenylamine (m. pt. 139° - 141°) was obtained using equimolecular quantities of the reagents.

Preparation of 2-amino-7-methoxyphenazine.



2 Gms. of 2,4-dinitro-4'-methoxydiphenylamine were hydrogenated in 160 ml. of absolute alcohol at 40 lbs. per sq. in. in the presence of 0.1 gms. of palladium-charcoal catalyst. The alcohol was evaporated at 40° under reduced pressure in a nitrogen atmosphere, leaving white crystals of 2,4-diamino-4'-methoxy-diphenylamine.

(i) 0.7 Gms. of 2,4-diamino-4'-methoxydiphenylamine was refluxed for 5 hours with a little m-dinitrobenzene and 50 ml. of nitrobenzene. 100 Ml. of 6 N hydrochloric acid were added to the cooled solution and the nitrobenzene then removed by steam distillation. The residue was filtered, the filtrate made alkaline and the precipitated product filtered off, washed, dried and found to have a melting point of 175° - 185°.

Recrystallised from water 450 mgm. (64%) of orange-red needles of 2-amino-7-methoxyphenazine of melting point 212° - 215° were recovered. Further recrystallisations raised the melting point to 217° - 220°.

Analysis:	C	H	N
$C_{13}H_{11}N_3O$ requires	69.31%	4.92%	18.65%
Found	68.50%	5.14%	18.35%

2-Amino-7-methoxyphenazine has an orange fluorescence. Dissolved in concentrated hydrochloric acid, a purple solution is obtained, turning red on dilution.

(ii) 1.2 Gms. of 2,4-diamino-4'-methoxydiphenylamine were refluxed for 1 hour with 18 gms. of powdered lead dioxide in 60 ml. of xylene. The lead dioxide was filtered from the hot solution and washed with a little hot xylene. The combined filtrate and washings were extracted with 6 N hydrochloric acid, the extract filtered, neutralised and the precipitate filtered off, washed and dried. A very poor yield of crude 2-amino-7-methoxyphenazine of melting point 203° - 209° was obtained. After recrystallisation from water a mixed melting point with a sample of prepared 2-amino-7-methoxyphenazine gave no depression of the melting point.

Preparation of 2-nitrodiphenylamine.

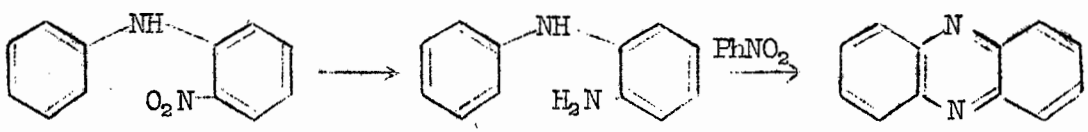
Compare F. Kehrmann and E. Havas. Ber. 341 (1913).

A 35% yield of 2-nitrodiphenylamine of melting point 72° - 75° was obtained.

Preparation of phenazine from 2-aminodiphenylamine.

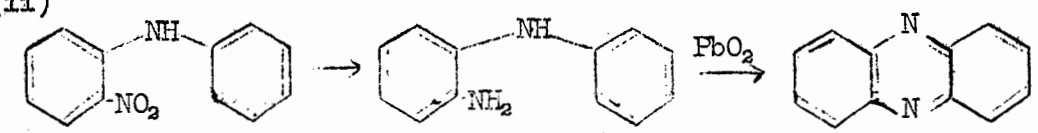
1 Gm. of 2-nitrodiphenylamine was hydrogenated in 75 ml. of absolute alcohol at 40 lbs. per sq. in. in the presence of 0.05 gms. of palladium-charcoal catalyst until the solution was practically colourless. The alcohol was evaporated in a nitrogen atmosphere under reduced pressure at about 40°.

(i)



The 2-aminodiphenylamine obtained by the hydrogenation of 1 gm. of 2-nitrodiphenylamine was refluxed for 5 hours with a little m-dinitrobenzene in 50 ml. of nitrobenzene, 100 ml. of 6 N hydrochloric acid added and the nitrobenzene removed by steam distillation. The cooled residue was filtered, the filtrate neutralised and the precipitated dark tarry product filtered off, washed, dried and vacuum sublimed. A small amount of orange yellow sublimate of melting point 80° - 150° was obtained. This sublimate contained a small amount of phenazine as was indicated by paper chromatograms using, butanol : concentrated hydrochloric acid = 4 : 1 saturated with water, and butanol : water: glacial acetic acid = 5 : 4 : 1 as eluting solvents.

(ii)



1 Gm. of 2-aminodiphenylamine was refluxed for 1 hour with 15 gms. of powdered lead dioxide in 60 ml. of xylene, the lead dioxide filtered off from the hot solution, washed with a little hot xylene and 100 ml. of 6 N hydrochloric acid added to the combined filtrate and washings. After removal of the xylene by steam distillation, the residue was filtered and the filtrate made just alkaline. The precipitated product was filtered off, washed, dried and found to have a melting point of 145° - 155°.

This product was purified by vacuum sublimation when a very small amount of phenazine of melting point 169° - 171° was obtained as a yellow sublimate.

Preparation of 2,2'-dinitrodiphenylamine.

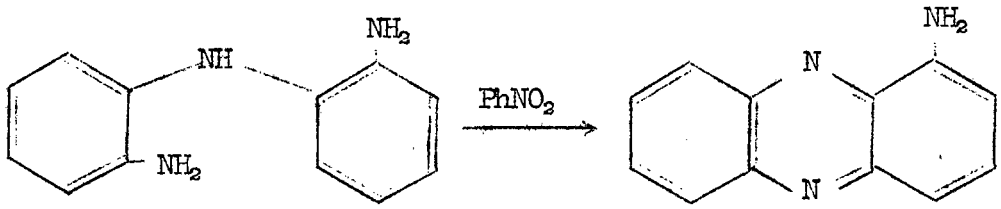
Compare Eckert and Steiner. Monatshifte für Chemie, 35, 1154.

A 25% yield of 2,2'-dinitrodiphenylamine (m. pt. 167° - 169°) was obtained.

Preparation of 1-aminophenazine from 2,2'-diaminodiphenylamine.

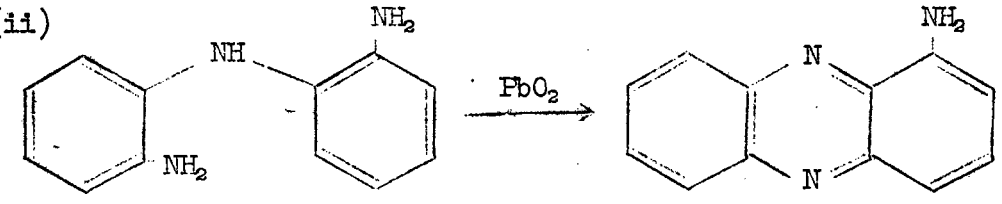
2 Gms. of 2,2'-dinitrodiphenylamine were hydrogenated in 150 ml. of absolute alcohol, at 40 lbs. per sq. in., in the presence of 0.1 gms. of palladium-charcoal catalyst until the solution was practically colourless. The alcohol was then evaporated under reduced pressure at about 40°, in a nitrogen atmosphere, leaving a dark tar of 2,2'-diaminodiphenylamine, which on standing gave white crystals.

(i)



Approximately 1 gm. of 2,2'-diaminodiphenylamine was refluxed for 5 hours with a little m-dinitrobenzene in 50 ml. of nitrobenzene, cooled, 100 ml. of 6 N hydrochloric acid was added and the nitrobenzene removed by steam distillation. The residue after steam distillation was filtered, the filtrate made alkaline and the red precipitate filtered off, washed and dried. This crude compound of melting point 148° - 160° was recrystallised by dissolving in boiling alcohol, adding water to the point of incipient precipitation, filtering and cooling. 500 Mgm. (± 50%) of 1-aminophenazine of melting point 162° - 167° were obtained. After subsequent recrystallisation from methanol, this product gave no depression of the melting point on admixture with a sample of known 1-aminophenazine.

(ii)



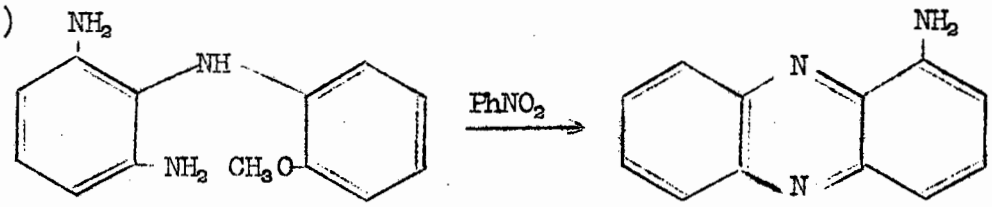
Approximately 1 gm. of 2,2'-diaminodiphenylamine was refluxed for 1 hour with 15 gms. of powdered lead dioxide in 60 ml. of xylene. The lead dioxide was filtered off from the hot solution and washed with a little hot xylene. 100 Ml. of 6 N hydrochloric acid was added to the combined filtrate and washings and the xylene removed by steam distillation. The residue after steam distillation was filtered, the filtrate neutralised and the precipitated product filtered off. A small yield of a dark dirty looking product of melting point 115° - 140° was obtained. The presence of a little 1-aminophenazine was proved by paper chromatograms using

(a) Butanol : concentrated hydrochloric acid = 4 : 1 saturated with water, and

(b) Butanol : water : acetic acid = 5 : 4 : 1 as solvents, comparing with a sample of known 1-aminophenazine.

Ring closure of 2,6-diamino-2'-methoxydiphenylamine.

(i)



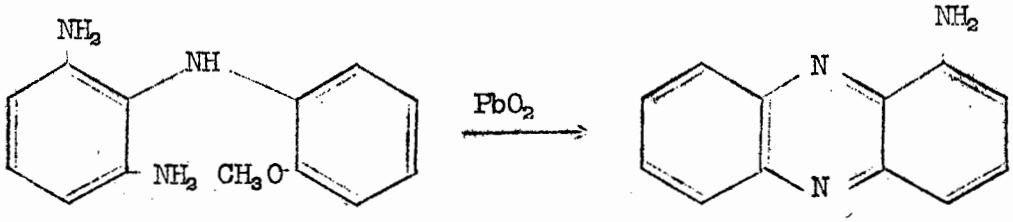
1.3 Gms. of 2,6-diamino-2'-methoxydiphenylamine (p.192) were refluxed for 5 hours in 65 ml. of nitrobenzene with a little m-dinitrobenzene. After cooling 100 ml. of 6 N hydrochloric acid were added and the nitrobenzene removed by steam distillation. The cooled residue was filtered, the filtrate made alkaline and the precipitate filtered off, washed and recrystallised from water. A dark red product of melting point 123° - 138° was obtained.

Paper chromatograms of this product compared with 1-aminophenazine, using as eluting solvents

(i) Butanol : concentrated hydrochloric acid = 4 : 1 saturated with water, and

(ii) Butanol : water : acetic acid = 5 : 4 : 1, showed the presence, in this product, of 1-aminophenazine.

(ii) (a)



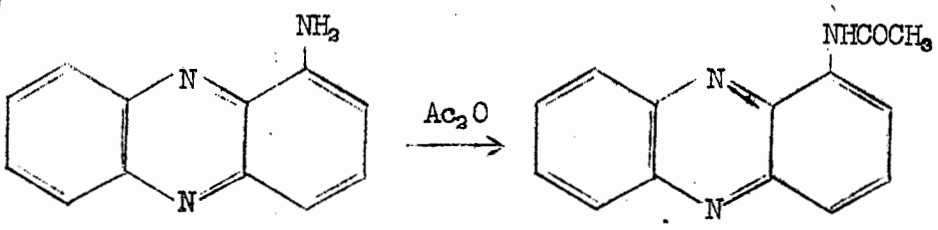
1.1 Gms. of 2,6-diamino-2'-methoxydiphenylamine were refluxed for 20 minutes in 33 ml. of xylene with 15 gms. of lead dioxide. The lead dioxide was filtered from the hot solution and washed with a little hot xylene. The combined filtrate and washings were extracted with 6 N hydrochloric acid, the blue acid extract filtered, the residue washed with a little 6 N hydrochloric acid and water, and the combined filtrate and washings neutralised with sodium hydroxide solution. After filtering off, washing and drying the red precipitate it was found to have a melting point of 154° - 160°. Recrystallised from water 400 mgm. (43%) of 1-aminophenazine of melting point 166° - 172° were obtained as fine red needles.

Subsequent recrystallisations raised the melting point to 169° - 172°.

Analysis:	C	H	N
$C_{12}H_9N_3$ requires	73.84%	4.65%	21.53%
Found	72.63%	4.55%	21.35%

No depression of the melting point was observed on admixture with a sample of known 1-aminophenazine.

(b)



400 Mgm. of this 1-aminophenazine were dissolved in approximately 15 ml. of acetic anhydride, well shaken up and allowed to stand at room temperature overnight. The reaction mixture was poured into water and the precipitated yellow product filtered off, washed, dried and recrystallised from alcohol to give golden needles of 1-acetamidophenazine of melting point 170° - 172°.

Analysis:	C	H	N
$C_{14}H_{11}N_3O$ requires	70.84%	4.67%	17.70%
Found	69.73%	4.64%	17.68%.

No depression of the melting point was observed on doing a mixed melt of this product with a sample of known 1-acetamidophenazine.

The observation in this preparation, that the methoxy group is eliminated in preference to a hydrogen atom and the ring closed in that position, is similar to that of McCombie et al[34]. They obtained phenazine on heating 2-amino -2'-methoxydiphenylamine with lead dioxide in the absence of a solvent.

SUMMARY.

1-Methoxyphenazine was nitrated and from the resultant 1-methoxy-4-nitrophenazine a number of previously unknown 1,4-substituted phenazines were prepared. A short series of similarly substituted phenazines was developed from the nitration product of 1-acetamidophenazine.

That the orientation of the two substituents in both series was the same and was 1,4-, was proved by chemical interconversions and by the successful preparation of the known 1,4-dihydroxy- and 1,4-diacetoxyphenazine.

3-Methoxy-o-quinone was condensed with 3-nitro- and 4-nitro-o-phenylenediamine to give 1-methoxy-5(or 8)-nitrophenazine and 1-methoxy-6(or 7)-nitrophenazine respectively. Similar condensations could not be achieved with 4-methoxy-o-quinone.

A number of trinitro-methoxydiphenylamines were prepared with two nitro groups in the 2,2'-positions, the other nitro group in the 4 or 6 position and the methoxy group in the 4 or 6 position. These compounds were converted to the corresponding triamines and attempts made to bring about ring closure by a variety of methods in order to synthesize amino-methoxyphenazines. It was found that with an amino group para to the diphenylamine linkage the ring closure could not be achieved.

2,6,2'-Triamino-4'-methoxydiphenylamine was successfully ring closed by the oxidative action of ferric chloride in dilute hydrochloric acid to give 1-amino-6-methoxyphenazine and from this compound a series of new phenazines was developed.

A reductive ring closure of 2,4-dinitrodiphenylamine and of 2,4-dinitro-4'-methoxydiphenylamine was attempted. In the first case a small amount of 2-nitrophenazine was formed. In both cases the presence of 2-aminophenazine was detected amongst a number of products of the reaction.

An attempted ring closure of 2,6-diamino-2'-methoxydiphenylamine, by heating with lead dioxide only, according to the method of Fischer and Heiler, was not successful. The procedure was modified by doing the reaction in an inert solvent. By this procedure 1-aminophenazine was obtained in good yield. This modified procedure was then employed for the successful preparation of a number of other phenazines.

A new method of phenazine synthesis was developed whereby 2,4'-diaminodiphenylamines were converted to 2-aminophenazines, in good yield, by heating with nitrobenzene and a little m-dinitrobenzene. This method was also successful for the conversion of 2,2'-diaminodiphenylamine to 1-aminophenazine and 2,4-diamino-4'-methoxydiphenylamine to 2-amino-7-methoxyphenazine in good yields. By this method 1-methoxy-6-aminophenazine, not obtained by other methods attempted, was synthesised.

The absorption spectra of the compounds prepared was determined in the range of 220 - 600 mμ and is briefly surveyed.

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SUMMARY.

The Li strain of Pseudomonas aeruginosa produces in suitable media two main red pigments, referred to as pigments A and B. The cultures of these organisms go through various yellow colour stages before red pigmentation results. Attempts have been made to establish the order in the formation of these red pigments, but only a possible sequence could be suggested.

In order to study the conditions for optimum production of red pigments some means of determining these quantitatively had to be developed. A good separation of pigments A and B has been achieved by means of paper chromatography, this forming the basis for their quantitative evaluation.

Pigment production by these organisms is variable, whole batches of cultures often producing none, or only little, of the red pigments. Subculturing the bacteria on agar-slopes resulted in a marked decrease in red pigmentation, which could, however, be restored to its original value by passing the organisms through certain media. Because of this variability it was found necessary to make dried pellets of the Li strain of Pseudomonas aeruginosa in order to standardise as far as possible the bacteria to be able to compare various findings at different times.

In attempting to find a large scale method for the production of the two red pigments, it was found that the organisms were extremely sensitive to the oxygenation conditions under which they grow, optimum red pigmentation taking place in shallow static aerobic cultures. The

relative amounts of the two individual pigments produced in cultures of these organisms have been shown to depend largely on the oxygenation conditions, the formation of pigment A being favoured by an increased supply of air, or by the inclusion of a chemical source of oxygen into the medium, the yield of pigment B being hardly affected under these conditions. Microaerophilic cultures, on the other hand, resulted in the production of pigment B only.

The possibility that pigments A and B are interconvertible when added separately to an actively growing culture, grown under oxygenation conditions which favour their individual formation, was investigated. Some of the findings indicate that the organisms can convert pigment A to pigment B when employing a medium lacking glycine.

Growth and red pigment production was found to depend very much on the composition of the medium in which the organisms of the Li strain of P s e u d o m o n a s a e r u g i n o s a grow. The ions, Mg, SO_4, K, PO_4 and Fe have been found essential for good red pigment formation, the various amino acids and carbon sources present in the medium greatly affecting the yields of pigments A and B.

The pH changes which take place in cultures where red pigment production is good are similar, their pH curves all showing two or three depressions which appear to be due to the formation of a number of products, including the precursors of pigment A and B and the red pigments themselves. The production of pigment A always takes place between a pH of 8.0 and 8.5, pigment B being present in maximum amounts only when the cultures have reached their highest pH, a stage when the respiration rate of the culture has dropped to about zero.

The behaviour of some of the many variants of the L-strain of *Pseudomonas aeruginosa* has been studied and reported on.

SUMMARY.

1-Methoxyphenazine was nitrated and from the resultant 1-methoxy-4-nitrophenazine a number of previously unknown 1,4-substituted phenazines were prepared. A short series of similarly substituted phenazines was developed from the nitration product of 1-acetamidophenazine.

That the orientation of the two substituents in both series was the same and was 1,4-, was proved by chemical interconversions and by the successful preparation of the known 1,4-dihydroxy- and 1,4-diacetoxyphenazine.

3-Methoxy-o-quinone was condensed with 3-nitro- and 4-nitro-o-phenylenediamine to give 1-methoxy-5(or 8)-nitrophenazine and 1-methoxy-6(or 7)-nitrophenazine respectively. Similar condensations could not be achieved with 4-methoxy-o-quinone.

A number of trinitro-methoxydiphenylamines were prepared with two nitro groups in the 2,2'-positions, the other nitro group in the 4 or 6 position and the methoxy group in the 4 or 6 position. These compounds were converted to the corresponding triamines and attempts made to bring about ring closure by a variety of methods in order to synthesize amino-methoxyphenazines. It was found that with an amino group para to the diphenylamine linkage the ring closure could not be achieved.

2,6,2'-Triamino-4'-methoxydiphenylamine was successfully ring closed by the oxidative action of ferric chloride in dilute hydrochloric acid to give 1-amino-6-methoxyphenazine and from this compound a series of new phenazines was developed.

A reductive ring closure of 2,4-dinitrodiphenylamine and of 2,4-dinitro-4'-methoxydiphenylamine was attempted. In the first case a small amount of 2-nitrophenazine was formed. In both cases the presence of 2-aminophenazine was detected amongst a number of products of the reaction.

An attempted ring closure of 2,6-diamino-2'-methoxydiphenylamine, by heating with lead dioxide only, according to the method of Fischer and Heiler, was not successful. The procedure was modified by doing the reaction in an inert solvent. By this procedure 1-aminophenazine was obtained in good yield. This modified procedure was then employed for the successful preparation of a number of other phenazines.

A new method of phenazine synthesis was developed whereby 2,4'-diaminodiphenylamines were converted to 2-aminophenazines, in good yield, by heating with nitrobenzene and a little m-dinitrobenzene. This method was also successful for the conversion of 2,2'-diaminodiphenylamine to 1-aminophenazine and 2,4-diamino-4'-methoxydiphenylamine to 2-amino-7-methoxyphenazine in good yields. By this method 1-methoxy-6-aminophenazine, not obtained by other methods attempted, was synthesised.

The absorption spectra of the compounds prepared was determined in the range of 220 - 600 mμ and is briefly surveyed.